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When, *Where* and *Why*

do newborns not only get sick but also die in Sao Tome & Principe?

Analysis of causes and risk factors contributing to perinatal and neonatal morbidity and mortality in a developing country – a case–control study

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Dissertation presented to fulfil the requirements necessary to obtain a PhD degree in Tropical Medicine

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Analysis of causes and risk factors contributing to perinatal and neonatal morbidity and mortality in a developing country – a case–control study

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SCIENTIFIC PUBLICATIONS ASSOCIATED TO THIS RESEARCH

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Articles published in peer reviewed international journals:

1 | **Vasconcelos A**, Bandeira N, Sousa S, Pereira F, Machado MC. Adolescent pregnancy in Sao Tome and Principe: a cross-sectional hospital-based study. BMC Pregnancy Childbirth. 2022;22(1):332.
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2 | **Vasconcelos A**, Bandeira N, Sousa S, Machado MC, Pereira F. Adolescent pregnancy in Sao Tome and Principe: are there different obstetric and perinatal outcomes? BMC Pregnancy Childbirth. 2022;22(1):453.
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3 | **Vasconcelos A**, Sousa S, Bandeira N, Alves M, Papoila AL, Pereira F, Machado MC. Antenatal screenings and maternal diagnosis among pregnant women in Sao Tome & Principe-Missed opportunities to improve neonatal health: A hospital-based study. PLOS Global Public Health. 2022;2(12): e0001444..
Available from: https://doi.org/10.1371/journal.pgph.0001444

4 |**Vasconcelos A**, Sousa S, Bandeira N, Alves M, Papoila AL, Pereira F, Machado MC. Determinants of antenatal care utilization – contacts and screenings – in Sao Tome & Principe: a hospital-based cross-sectional study. Arch Public Health. 2023;81:107. Available from: https://doi.org/10.1186/s13690-023-01123-1

5 | **Vasconcelos A**, Sousa S, Bandeira N, Alves M, Papoila AL, Pereira F, Machado MC. Intestinal parasitic infections, treatment and associated factors among pregnant women in

Sao Tome and Principe: A cross-sectional study. J Trop Med. 2022;2022:7492020. Available from: http://dx.doi.org/10.1155/2022/7492020

6 | **Vasconcelos A**, Sousa S, Bandeira N, Alves M, Papoila AL, Pereira F, Machado MC. Adverse birth outcomes and associated factors among newborns delivered in Sao Tome & Principe: a case–control study. PLoS ONE. 2023;18(7):e0276348.
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Manuscripts submitted to peer review international journals:

i | **Vasconcelos A,** Sousa S, Bandeira N, Alves M, Papoila AL, Pereira F, Machado MC. Intestinal parasitic infections and adverse outcomes among pregnant women and their newborns in Sao Tome & Principe: a hospital-based cross-sectional study.
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ii | **Vasconcelos A**, Sousa S, Bandeira N, Alves M, Papoila AL, Pereira F, Machado MC. Factors associated with perinatal and neonatal mortality in Sao Tome & Principe: a prospective cohort study.
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SCIENTIFIC COMMUNICATIONS

To comply with regulation nº 474/2012 of the 3rd cycle courses of the Instituto de Higiene e Medicina Tropical – Universidade NOVA de Lisboa (IHMT-NOVA), the following annual public presentation of the results of this thesis was performed:

2016 [Oral presentation] at the 7.as Jornadas Científicas do IHMT-NOVA. Title: Thesis-protocol study.

2017 [Poster] at the 8.as Jornadas Científicas do IHMT-NOVA. Title: Thesis 2017 results.

2018 [Poster] at the 9.as Jornadas Científicas do IHMT-NOVA. Title: Thesis 2018 Results.

2019 [Oral presentation] at the X Jornadas Científicas do IHTM-NOVA. Title: Why, When and Where do newborns not only get sick but also die in Sao Tome & Principe? Analysis of causes and risk factors contributing to Perinatal and Neonatal Morbidity and Mortality in a developing country – a case-control study

2021 [Oral presentation] at the XII Jornadas Científicas do IHMT-NOVA. Title: Adolescent pregnancy in Sao Tome & Principe: are there different obstetric and perinatal outcomes?

2022 [Flash-Poster] at the XIII Jornadas Científicas do IHMT-NOVA. Title: Intestinal parasitic infections in pregnant women in Sao Tome & Principe: are there adverse outcomes? a cross-sectional study

Oral Communications in national conferences:

2017 | 4º Congresso Nacional de Medicina Tropical (4º CNMT) IHMT-NOVA. Lisbon 19th to 21st April.

2018 | Global Health & Tropical Medicine (GHTM). IHMT-NOVA. Lisbon 15th November.

2018 | Seminário de Doutorandos IELT-FCSH NOVA. Penélope corre ao encontro de Ulisses_O tempo da investigação I: Para uma gestão do tempo e dos métodos de trabalho. Edifício I&D NOVA, Lisbon 5th December.

2023 | IV Encontro Luso Brasileiro de Avaliação em Saúde, Gestão e Translação do Conhecimento no âmbito da CPLP: da teoria à prática - 6.º Congresso Nacional de Medicina Tropical (6º CNMT) IHMT-NOVA. Mães e seus recém-nascidos em São Tomé e Príncipe: "tracing the invisible". Lisbon, 19th of April.

2023 | 6.º Congresso Nacional de Medicina Tropical (6º CNMT) IHMT-NOVA. Adverse birth outcomes and associated factors among newborns delivered in Sao Tome & Principe: a case–control study. Lisbon, 20th of April.

Oral Communications in international conferences:

2022 | 5th GLOBEHEAL Global Public Health Conference 2022 – Future of Global Health in a Changing World – 24th and 25th February 2022 (virtual conference) presented **three** oral communications:

1 |Antenatal care in Sao Tome & Principe: beyond the number of visits.

2 | Pregnant women´s profile: are there differences in antenatal care in Sao Tome & Principe.

3 | Adolescent pregnancy in Sao Tome & Principe: are there different obstetric and perinatal outcomes?

AWARD |

The author was recognized as one of the best oral communications of GLOBEHEAL 2022 (Appendix 1) with the oral communication "Antenatal care in Sao Tome & Principe: beyond the number of visits"

Poster presentations [7]

The partial results of this PhD thesis were also presented at the following conferences:

2017 | 18º Congresso Nacional de Pediatria, Alfândega do Porto. 25-27 October 2017, Oporto, Portugal.

2018 | Encontro Ciência 2018. Encontro com a Ciência e Tecnologia em Portugal (Fundação para a Ciência e a Tecnologia). Centro de Congressos de Lisboa. 2-4 July 2018, Lisbon, Portugal.

2018 | Ninth EDCTP Forum – Clinical research and sustainable development in sub-Saharan Africa: the impact of North-South partnerships. Fundação Calouste Gulbenkian, Lisboa. 17-21 September 2018, Lisbon, Portugal.

2019 | 2nd world Congress on Maternal Fetal Neonatal Medicine. 4 - 6 April 2019, London, United Kingdom.

2019 | 5º Congresso Nacional de Medicina Tropical (5ºCNMT) IHMT-NOVA. 10-12 April 2019, Lisbon, Portugal.

2019 | Encontro Ciência 2019. Encontro com a Ciência e Tecnologia em Portugal (Fundação para a Ciência e a Tecnologia). Centro de Congressos de Lisboa. 8-9 July 2019, Lisbon, Portugal.

2019 | NOVA Science Day 2019 – 2º Encontro de Ciência da NOVA – Reitoria da Universidade Nova de Lisboa. 18 September 2019, Lisbon, Portugal.

Co-author

2017 | [Poster communication with discussion]
18º Congresso Nacional de Pediatria, Alfândega do Porto. 25-27 October 2017, Oporto, Portugal.
PD-114 - (18SPP-4526) - Internamentos em idade pediátrica no Hospital Central de São Tomé e Príncipe (2015-2016)
Sequeira A, **Vasconcelos A**, Sousa S, Almeida F, Pereira P, Machado MC

2023 | [Abstract submitted to be presented as a poster communication]
ESPID 41st Annual Meeting of the European Society for Paediatric Infectious Diseases. Lisbon 8-14th May 2023. Portugal.
Neonatal sepsis in a resource-constrained country without blood cultures
Vasconcelos J, Vaz B, Sousa S, Alves M, Papoila AL, **Vasconcelos A**

PROPOSALS FOR FUTURE PROJECTS

Positive **A**ir

Implementation, training, and maintenance of bubble CPAP in the neonatal care unit of Sao Tome & Principe to improve outcomes for neonates with respiratory distress.

Proposal submitted to the 2022 Children's Prize Children's Prize (childrensprize.org)

The PhD researcher was invited to participate in the 2022 Children´s Prize **Round 2** Prize Plan.

Positive Air was selected over 200 applications from over 45 countries and was one out of 10 Round 1 applications passed on to Round 2.

Positive Air was **one of the finalists**, classified as among the strongest received but the judging committee chose another project as 2022 prize year´s winner.

(Appendix 2)

Kangaroo **M**other **C**are **and premature babies care improvement**

Proposal for an intervention in the Neonatal Care Unit in Sao Tome & Principe.
The PhD researcher in collaboration with the HAM Paediatric Department submitted a project to be funded by the Portuguese Government (Camões, I.P.) aiming to introduce this method and to scale up the care of premature babies at the NCU in HAM.
(Appendix 3)

Ongoing research

Additional research projects are being conducted/prepared on neonatal postpartum care in the country to identify main gaps (Appendix 4 and 5).

To my daughter **Laura,** affectionately known as “Here comes the Sun”.

She was born to the sound of this magical Beatles song, and since then she has been bringing me the sun that shines every day.

ACKNOWLEDGEMENTS

This PhD has made me feel as if I have undergone a “pregnancy” – and a long one! Along the way, I encountered obstacles and some unpredictable challenges, but ultimately, I successfully delivered this…thesis. However, this would not have been possible without the many “superheroes,” whose support I relied on to bring this “child” to term, and to whom I would like to extend my heartfelt gratitude.

This “gestation” would not have been possible without the mentorship of my excellent supervisors.

My supervisor, Professor Maria do Céu Machado, provided invaluable support, guidance, and encouragement throughout the period of my PhD. Her strength, persistence, relentless energy, integrity, knowledge and vision are a consistent inspiration in my life. Meeting her, in 2003, motivated me to become a Paediatrician, and it is her example that I follow. She is, to me, my "Mother" in the paediatric world, and I am profoundly grateful for these twenty years of mentorship. Much more is yet to come!

My life would have been very different had it not been for Professor João Luís Baptista. In 2002, I was lucky to have been part of a group of final year medical students that he took to Mozambique to carry out a field study on sexually transmitted diseases. This trip changed my life, and Professor Baptista awakened in me a curiosity and connection with Africa that I had never realised were in me. I would not have embarked on this journey into Tropical Medicine if it had not been for that life-changing experience! Despite no longer being with us, I put many of his teachings into practice and am always mindful of the priorities he instilled in me. As my co-supervisor, his guidance at the beginning of this thesis was invaluable. I know that he would be very proud that we reached a successful conclusion of this PhD research. I miss you, your strength, your feverish enthusiasm, and faith in a better future for Africa!

I am deeply grateful to my dear co-supervisor, and friend, Professor Filomena Pereira, who was a pillar throughout this PhD and who tirelessly provided me with all the opportunities and tools that enabled me to achieve an ever-higher standard. I am thankful

for her guidance and positive that more challenges and adventures are still to come. This is only the beginning.

I thank Professor Ana Luísa Papoila for the insightful discussion on different aspects of this research, from statistical analysis to critical feedback on research papers. I also extend my deep gratitude to Marta Alves for crucial advice, her work on data analysis and for her critical feedback and precision in checking all statistical data and results.

I would also like to thank the other members of my advisory committee, Professor Jorge Atouguia and Professor Inês Fronteira, for their constructive feedback, which greatly improved my research proposal. I would particularly like to thank Professor Jorge Atouguia for all the important teachings in Tropical Medicine, guidance on my PhD proposal, and for encouraging me to choose a "research-paper-style" PhD. And, of course, for believing that I would have the energy and resilience with which to carry it out.

I especially want to thank and acknowledge the generous inputs of my special friends that read and commented on this thesis. Helena Isabel Almeida and Nat Marshall, I am grateful for your help.

I am profoundly indebted to all the women who participated in the study. You shared with me your life stories, anxieties and lessons on how to savour all the little joys life brings. I offer a special embrace to all the mothers who have lost their babies. Preventing other women from having to endure the painful experiences and profound losses that you have is the cornerstone of this research.

Having easy access to all the latest cutting-edge technologies and facilities makes it so much easier to be an excellent healthcare professional; but when that is not the case, when even basic supplies are scarce or unavailable, that is the real challenge. My deep appreciation goes out to all the midwives and doctors who work daily in challenging conditions at Hospital Dr. Ayres de Menezes. I would especially like to thank doctors Nelson Bandeira and Swasilanne Sousa, and chief-nurse Paulina Oliveira. There are no words to describe Dr. Nelson's wholehearted dedication to his role as obstetrician in the maternity ward. His commitment and dedication to all pregnant women contribute significantly to the reduction of maternal and neonatal mortality in the country. And Swasy, my friend, it has been 14 years of working together to improve the health of

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To Dominguês and Joel, my "sons" from Sao Tome & Principe, you both brought so much flavour to my life, even when it was bitter-sweet, and hard to swallow. Your life stories and examples will one day be written, I promise.

Sao Tome & Principe has my heart, and I feel its calling, almost every day. The *"leve-leve"* country, a phrase deeply ingrained in the country´s culture, often used to convey a relaxed and laid-back attitude towards life! Not always light *"leve-leve"* but deeply connected with the real essence of life itself. This country has given me so much…

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distress. I will never forget when I telephoned you at midnight from the middle of the Ugandan jungle, when I was truly scared, and you made me laugh out loud!

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To my Nana, the unconditional love you gave me was always a source of energy. Thank you so much for everything you offered me. I know that you still protect me every day!

To all my female ancestors.
You are an inspiration and made it possible for me to choose a different path in life!

To my dear grandmother, who is now 98 years old and who has made me promise to hold my thesis presentation while she is here. I pledge that I will, and there is a seat reserved for you in the front row, for sure. You are my Queen Mother, and I am very proud of your example.

And finally, to Laura. Thank you, my beautiful daughter and partner, who weathered all the difficult times with me on this journey and gave me fresh hope and energy to battle through for another day. We started this PhD when I was carrying you in my belly, and you were also very interested in the tropical classes. When you were only two years old, we went to our first field study period in Sao Tome & Principe, and I dropped you off at your very first preschool there, so I could work at the hospital. What an unusual and adventurous childhood you are having!
You are such a wonderful and unique bright human being, and I am deeply blessed and honoured to be your mother.

Thank you for everything!

Background: Neonatal mortality reduction is a global goal, but its factors vary based on country-specificities. In Sao Tome & Principe (STP), neonatal deaths account for 48% of under-five-deaths, but major knowledge gaps exist. This is the first study conducted in neonatal health in STP and aims to answer *"when, where and why"* do newborns (including stillbirths) die, adverse birth outcomes (ABOs) and associated factors.

Methods: Hospital-based-research conducted with randomly recruited pregnant women admitted for delivery. For perinatal and neonatal death analysis, a prospective-cohort study was performed, in which the mother-newborn-dyads were evaluated after the 28th day (n=194). To study the ABOs a case-control study was performed (n=519): newborns with one or more ABO were the cases (n=176), healthy newborns the controls (n=343). Additionally, a retrospective study of pregnant women´s antenatal care (ANC) cards (n=511) and cross-sectional-studies comparing women with adequate ANC utilization (n=213) to those with partial utilization (n=232); pregnant teenagers ≤19 years (n=104) with pregnant adults (n=414); pregnant women with an intestinal parasitic infection (IPI) (n=210) with noninfected-IPI (n=151) were conducted.
Logistic regression models were used, a p-value<0.05 was considered statistically significant.

Findings: A total of 518 mothers and 535 births (34 twins) were enrolled. In the prospective cohort, the death-outcome-group (n=22) consisted of 72.7% (16) stillbirths (69% intrapartum), 18.2% (4) early and 9.1% (2) late neonatal deaths (probability of 30 stillbirths per 1000 livebirths, and neonatal mortality rate range between 11-31). Factors significantly associated with mortality were high-risk-pregnancy [cOR 2.91, 95% CI:1.18-7.22], meconium-stained-fluid [cOR 4.38, 95% CI:1.74–10.98], prolonged rupture of membranes [cOR 4.84, 95% CI:1.47–15.93], transfer from another unit [cOR 6.08, 95% CI:1.95–18.90], and instrumental delivery [cOR 8.90, 95% CI:1.68–47.21]. From the case-control study, 66% (n=343) healthy newborns and 34% (n=176) with ABOs were identified: 17.7% (92) preterm, 16% (83) low-birth-weight, 8.1% (42) birth asphyxia, 4% (21) sepsis suspicion and 1.5% (8) congenital anomalies. Twin pregnancy [aOR 4.92, 95% CI:2.25–10.74], prolonged rupture of membranes [aOR 3.43, 95% CI:1.69–6.95], meconium-stained-fluid [aOR 1.59, 95% CI:0.97-2.62], and <8 contacts [aOR 0.33, 95% CI:0.18–0.60] were significantly associated with ABOs. Concerning ANC, 81% had ≥4 contacts, 38.7% ≥8, 51.7% started during the first trimester. ANC screening-tests absence was found in a 24%-41% range, 36% due to lack of money. Main ANC problems were IPI (59.2%), bacteriuria (43.2%) and anaemia (37%). Pregnancy at a very-early-age (≤15) was experienced by 7.7%, with an overall adolescent pregnancy prevalence of 20.1%. The ABOs imputable to adolescent births were foetal distress [cOR 1.94, 95% CI:1.18–3.18] and performance of neonatal resuscitation manoeuvres [cOR

2.4, 95% CI:1.07–5.38]. The overall prevalence of IPI (95% CI:52.9-63.3), was mainly due to helminthiasis (55.9%). *Schistosoma intercalatum* and *Entamoeba histolytica* were found in 3.0% and 1.9%, respectively. ABOs for IPI-mothers compared with non-IPI showed no statistically significant difference.

Conclusion: Perinatal and neonatal deaths were up to two-times higher. Unexpectedly, most were stillbirths; thus, the triple-*Wh*-answers: *when do they die (livebirths and stillbirths)?* during labour, *where*? in the maternity unit, and *why*? due to intrapartum-complications. Modifiable factors were identified, mainly intrapartum red-flags, and should be prioritized in cost-effective interventions.

Keywords: neonatal mortality, stillbirths, adolescent pregnancies, antenatal care, intestinal parasitic infections, intrapartum complications, low- and middle-income countries, Sao Tome & Principe

Introdução: A redução da mortalidade neonatal é um objetivo global, mas os seus fatores variam com o contexto de cada país. Em São Tomé e Príncipe (STP), a mortalidade neonatal representa 48% das mortes de menores de cinco anos, mas existe uma importante lacuna de conhecimento. Este é o primeiro estudo em saúde neonatal de STP e tem como objetivo responder a *"quando, onde e porquê*" os recém-nascidos morrem (incluindo nados-mortos), quais os desfechos adversos ao nascimento (ABOs) e respetivos fatores associados.

Métodos: Estudo hospitalar realizado com grávidas internadas para o parto, recrutadas aleatoriamente. A análise das mortes perinatais/neonatais foi realizada numa coorte prospetiva, com as díades-mãe-bebé avaliadas após o 28º dia de vida (n=194). Os ABOs foram estudados por caso-controlo (n=519): recém-nascidos com ABOs (n=176) comparados com saudáveis (n=343). Um estudo retrospetivo dos boletins pré-natais da grávida (n=511) e os seguintes estudos transversais foram realizados: comparação entre mulheres com cuidados pré-natais adequados (n=213) e parcialmente adequados (n=232); grávidas adolescentes ≤19 anos (n=104) e adultas (n=414); grávidas com infeção parasitária intestinal (IPI) (n=210) e sem infeção-IPI (n=151). Foram utilizados modelos de regressão logística, $p<0.05$ foi estatisticamente significativo.

Resultados: Mães (518) e 535 nascimentos (34 gémeos) foram incluídos. No estudo coorte, as mortes (n=22) foram: 72.7% (16) nados-mortos (69% intraparto), 18.2% (4) neonatais precoces e 9.1% (2) tardias (probabilidade de 30 nados-mortos por 1000 nados-vivos e intervalo de taxa da mortalidade neonatal entre 11-31). Fatores significativamente associados à mortalidade foram gravidez de alto-risco [cOR 2.91, IC 95%:1,18-7,22], mecónio [cOR 4.38, IC 95%:1.74-10.98], rotura prolongada de membranas [cOR 4.84, 95% CI:1.47–15.93], transferência de outra unidade [cOR 6.08, IC 95%:1.95–18,90] e parto instrumental [cOR 8.90, IC 95%:1.68–47.21]. No estudo caso-controlo, 66% (n=343) dos recém-nascidos eram saudáveis e 34% (n=176) com ABOs: 17.7% (92) prematuros, 16% (83) baixo peso, 8.1% (42) asfixia, 4% (21) suspeita de sépsis e 1.5% (8) anomalias congénitas. Gravidez gemelar [aOR 4,92, IC 95%:2.25–10.74], rotura prolongada de membranas [aOR 3.43, IC 95%:1.69–6.95], mecónio [aOR 1.59, IC95%:0.97-2.62] e <8 consultas [aOR 0.33, IC 95%:0.18–0.60] foram significativamente associados a ABOs. Nos cuidados pré-natais, 81% tiveram ≥4 consultas, 38.7% ≥8, 51.7% início primeiro trimestre. Exames pré-natais não realizados entre 24%-41% das grávidas, 36% por motivos económicos. Principais diagnósticos pré-natais: IPI (59.2%), bacteriúria (43.2%) e anemia (37%). Gravidez precoce (≤15 anos) em 7.7%, prevalência de gravidez na adolescência de 20.1%. ABOs imputáveis a partos na adolescência: sofrimento fetal [cOR 1.94, IC 95%:1.18–3.18] e realização de manobras de reanimação neonatal [cOR 2.4, IC 95%:1.07–5.38]. A prevalência geral de IPI

(IC95%:52.9-63.3), foi principalmente devido a helmintíases (55.9%). *Schistosoma intercalatum* e *Entamoeba histolytica* foram encontrados em 3.0% e 1.9%, respetivamente. Mães-IPI comparadas com as não-IPI não apresentaram diferenças estatisticamente significativas em relação aos ABOs.

Conclusão: As mortes perinatais e neonatais foram até duas vezes superiores, inesperadamente a maioria foram nados-mortos. As respostas do triplo-*Wh: quando morrem (nados-vivos e nados-mortos)?* durante o parto, *onde?* na maternidade e *porquê?* devido a complicações intraparto. Foram identificados fatores modificáveis, principalmente sinais de alarme intraparto, que devem ser priorizados em intervenções custo-efetivas.

Palavras-chave: mortalidade neonatal, nados-mortos, gravidez na adolescência, cuidados pré-natais, infeções parasitárias intestinais, complicações intraparto, países de baixa e média renda, São Tomé e Príncipe

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CHAPTER 1 |

INTRODUCTION

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LIST OF ABBREVIATIONS

A

ABO	Adverse Birth Outcome
ANC	Antenatal Care
AOR	Adjusted Odds Ratio
APGAR	Appearance, Pulse, Grimace, Activity, and Respiration
ASB	Asymptomatic Bacteriuria

B

BEmONC	Basic Emergency Obstetric and Neonatal Care

C

CI	Confidence Interval
CEmOC	Comprehensive Emergency Obstetric Care
CPAP	Continuous Positive Airway Pressure
CRVS	Civil Registration and Vital Statistics System
CTG	Cardiotocography

D

DHS	Demographic and Health Survey

E

EmONC	Emergency Obstetric and Neonatal Care
ENAP	Every Newborn Action Plan
ENND	Early Neonatal Death
EOS	Early-Onset Neonatal Sepsis

F

FANC	Focused Antenatal Care programme
FIGO	International Federation of Gynaecology and Obstetrics

G

GA	Gestational Age
GBS	*Group B Streptococcus*
GDP	Gross Domestic Product

H

HAM	Hospital Dr. Ayres de Menezes
Hb	Haemoglobin
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HDN	Haemolytic Disease of Newborn
Hep-BD	Hepatitis B Birth-Dose Vaccination
HIC	High-Income Country
HIV	Human Immunodeficiency Virus

I

ICD	International Classification of Diseases
IHMT	Instituto de Higiene e Medicina Tropical
IMNCI	Integrated Management of Neonatal and Child Illnesses
IPI	Intestinal Parasitic Infections
IPTp-SP	Intermittent Preventive Treatment in Pregnancy with Sulfadoxine-Pirymethamine
IUGR	Intrauterine Growth Restriction
IVD	Instrumental Vaginal Delivery

L

LBW	Low Birth Weight
LLMIC	Low- and Lower-Middle-Income Country
LMIC	Low-Middle-Income Country
LNNDs	Late Neonatal Deaths
LOS	Late-Onset Neonatal Sepsis

M

MDG	Millennium Development Goals
MICS	Multiple Indicator Cluster Survey Series
MNCH	Maternal, Newborn, And Child Health Care
MOH	Major Obstetric Haemorrhage
MoH	Ministry of Health
MTCT	Mother-To-Child Transmission

N

NTDs	Neglected Tropical Diseases
NCU	Neonatal Care Unit
NNM	Neonatal Near-Miss
NMR	Neonatal Mortality Rate

O

OR	Odds Ratio

P

PALOP	Portuguese Speaking African Countries (Países Africanos de Língua Oficial Portuguesa)
PM2.5	Particulate Matter 2.5
PNC	Postnatal Care
PPH	Postpartum Haemorrhage
PROM	Prolonged Rupture of Membrane
PTB	Premature Baby

R

RDS	Respiratory Distress Syndrome
Rh	Rhesus
RhD	Rhesus factor D antigen

S

SBA	Skilled Birth Attendant
SDG	Sustainable Development Goals
SGA	Small for Gestational Age

	SRMNEA-N	Reproductive, Maternal, Newborn, Child, Adolescent And Nutrition Health Service
	SSA	sub-Saharan Africa
	STH	Soil-Transmitted Helminth
	STP	Sao Tome & Principe
T		
	TORCH	Toxoplasma gondii, 'other' infections, Rubella, Cytomegalovirus, and Herpes Simplex Infection
	TT-CV	Tetanus Toxoid-Containing Vaccine
K		
	KMC	Kangaroo Mother Care
U		
	U5MR	Under5 Mortality Rate
	UN	United Nations
	UN IGME	United Nations Inter-agency Group for Child Mortality Estimation
	UNICEF	United Nations Children's Fund
	UNL	Universidade Nova de Lisboa
	USD	United States Dollar
W		
	WASH	Water, Sanitation, and Hygiene
	WHO	World Health Organization

Note: Not all abbreviations used in this dissertation are commonly used and well-known; therefore, for clarity purposes, the abbreviation will be reintroduced and defined the first time the term is used in each section. The terms are also used interchangeably with the abbreviation when justified for enhancing reading comprehension.

GLOSSARY OF TERMS

Neonatal period extends from the time of birth to 28 days. The first week of life is called the early neonatal period, and 8 to 28 days is the late neonatal period.

Perinatal period is the time around the moment of birth. Conventionally, this time is limited to the period between 28 weeks gestation age and 1 week postnatally.

Early and late neonatal deaths (deaths among livebirths during the first 28 completed days of life) may be subdivided into early neonatal deaths, occurring during the first 7 days of life, and late neonatal deaths, occurring after the 7^{th} day but before the 28^{th} completed day of life.

Neonatal mortality rate (NMR) is the probability that a child born in a specific year or period will die during the first 28 completed days of life if subject to age-specific mortality rates of that period, expressed per 1000 livebirths.

Stillbirth is a baby born without any signs of life at or after 28 weeks of gestation or at least 1000 g in birth weight.

Perinatal Mortality Rate comprehends late foetal and early neonatal deaths weighing over 1000 g at birth expressed as a ratio per 1000 livebirths, that is, dead born foetus (stillbirth) and newborn deaths occurring in the first week of life (World Health Organization definition for nations with less well-established vital record systems). Early neonatal deaths plus stillbirths comprise perinatal mortality.

Under5 mortality rate (U5MR) is a core indicator for child health and well-being, representing the probability per 1000 that a newborn baby will die before reaching the age of five (0-59 months).

Maternal death is defined as the death of a woman while pregnant or within 42 days of termination of pregnancy from any cause related to or aggravated by pregnancy or its management.

Adverse birth outcomes (ABOs) refer to negative health outcomes that occur in newborn babies as a result of factors related to pregnancy, labour, or delivery. For this research, adverse birth outcomes were defined as premature birth (delivery before 37 weeks of gestation), low birth weight (less than 2500 grams), major birth defects (physical or developmental abnormalities present at birth), macrosomia (>4 kg birth weight), perinatal asphyxia (5-minute Apgar score <7), and probable sepsis (based on clinical criteria and risk factors).

Antenatal care (ANC), also known as prenatal care, refers to the healthcare services and support provided to pregnant women before the birth of their child, focused on monitoring and supporting the health of both the mother and the developing foetus throughout the pregnancy.

Adolescent pregnancy, also referred to as teenager pregnancy, refers to a pregnancy in a female between the ages of 10 and 19 years old.

Low- and lower-middle income countries (LMIC and LLMIC), low-resource countries/settings and sub-Saharan Africa (SSA) region or countries are often used interchangeably during this thesis, although there are differences between them.

A **low-resource country or resource-constrained** is typically defined as a nation with limited economic and technological development, often characterized by a lack of access to basic healthcare, education, and infrastructure. The term "low-resource country" is often used in discussions of global health and development, where it is recognized that many countries require external assistance to overcome these challenges and improve the well-being of their populations. It is important to note that the exact definition of a low-resource country can vary depending on the context and the specific indicators used to assess economic and social development.

STRUCTURE OF THE THESIS

This PhD thesis is structured in four chapters.

Chapter 1 | is the Introduction and consists of five parts. Part I is the state of the art featuring a literature review as background to this thesis. Part II debates the problem of data sources for neonatal mortality rates and high-impact solutions amenable to reducing neonatal deaths in resource-constrained countries. Part III introduces Sao Tome & Principe and data on neonatal and perinatal health, outcomes and associated factors available prior to this thesis. Part IV presents this thesis' rationale, aims and objectives. Part V lists the references cited in Chapter 1.

Chapter 2 | presents a brief summary of the material and methods used in the research.

Chapter 3 | includes the six published journal articles and two submitted manuscripts for peer review international journals. The eight articles/manuscripts are all interrelated and complement each other.

Chapter 4 | draws together the research findings across the articles and manuscripts providing a summative discussion, includes the strengths and limitations of this research, conclusions, policy implications and recommendations for future studies.

CHARTER 1 |

PART I | State of the art

1. The first 28 days of life

The beginning of life —the neonatal period—is the most at-risk time for a child's survival (1). A child is 46 times more likely to die within these 28 days than in the entire period from 28 days to five years of age (2). Furthermore, neonatal deaths are the main cause of the under5 mortality rate (U5MR), since 46% occur within the first 28 days of life, highlighting the importance of the neonatal period impact on overall child mortality (Figure 1) (3).

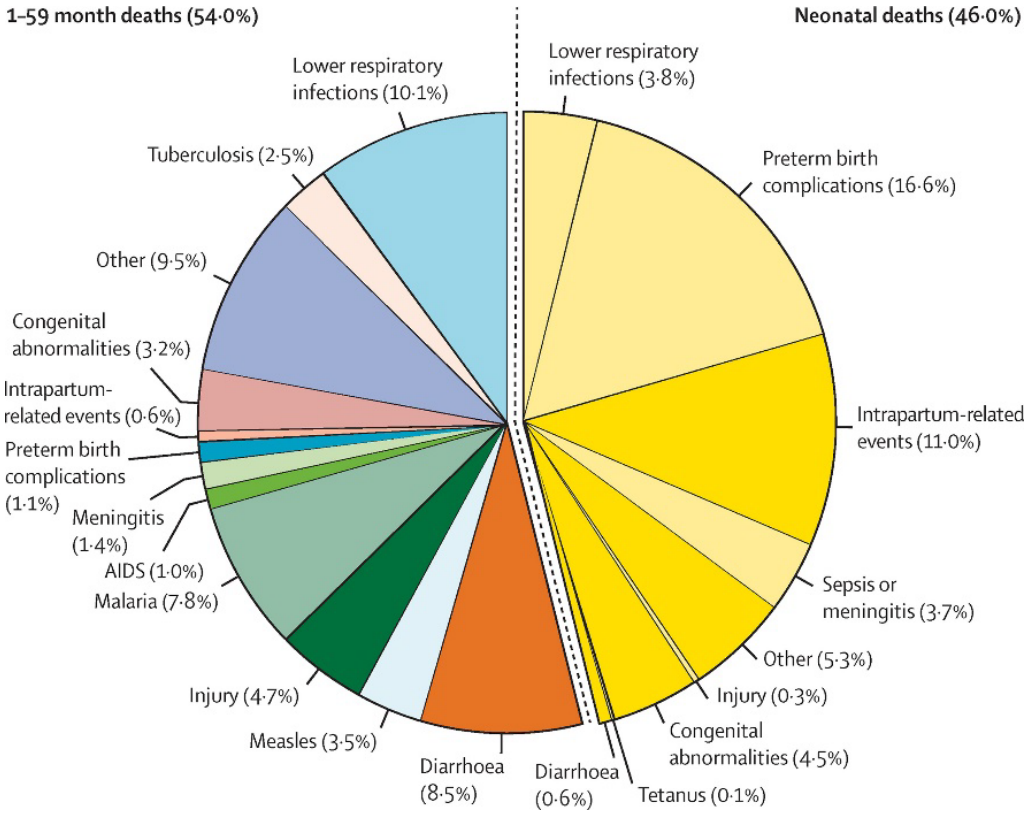


Figure 1 | Global causes of under5 deaths, 2019. Deaths of neonates (aged 0–27 days) and main neonatal adverse birth outcomes are on the right-hand side and deaths of children aged 1–59 months are on the left-hand side. (Image source: Global, regional, and national causes of under5 mortality in 2000–19: an updated systematic analysis with implications for the Sustainable Development Goals, Lancet 2021 (3), https://doi.org/10.1016/S2352-4642(21)00311-4 _licensed under CC BY 4.0)

In 2005, Lawn et al. published an article titled *"4 million neonatal deaths: When? Where? Why?"* that reviewed and analysed the main problems of newborns in low- and lower-middle income countries (LLMICs) (4).

Until then, newborn babies were left behind—invisible in the initial Millennium Development Goals (MDG) framework and received scant policy attention and investment (5). Stillbirths were entirely missed and still do not appear in the United Nations report for women's and children's health (6).

It is important to highlight that newborn deaths and stillbirths account for twice as many deaths as malaria and human immunodeficiency virus (HIV) infection combined, but have received much less attention and investment (7).

The following sections of Part I aim to update the answers to the triple ***Wh***: *Where? When? and Why*? do newborns die.

1.1. **Where** are newborn deaths happening?

Neonatal mortality is a global public health concern that is strikingly high in LLMICs, particularly, in sub-Saharan African (SSA) countries (8). The chance of survival is impacted by geographic location at birth, since there is still a significant number of babies that do not have access to health care services that meet their basic needs such as skilled birth attendance, prompt intervention for neonatal resuscitation, shelter, water, sanitation, and security (3, 8).

Approximately 53% of all neonatal deaths occur in the SSA region (8). A child born in SSA is, therefore, 10 times more likely to die in the first month than a child born in a high-income country (HIC), highlighting the staggering inequality between SSA countries and HICs (Figure 2 and Chart 1) (3, 8, 9).

Neonatal deaths in numbers

Mortality in the neonatal period, has been dropping at a much slower rate than in 1–59-month-olds, and 2.4 million newborns are still dying every year (3, 8). Globally, the neonatal mortality rate (NMR) in the last two decades has only dropped from 28·0 (26·8–29·5) deaths per 1000 livebirths in 2000 to 17·9 (16·3–19·8) in 2019 (8).

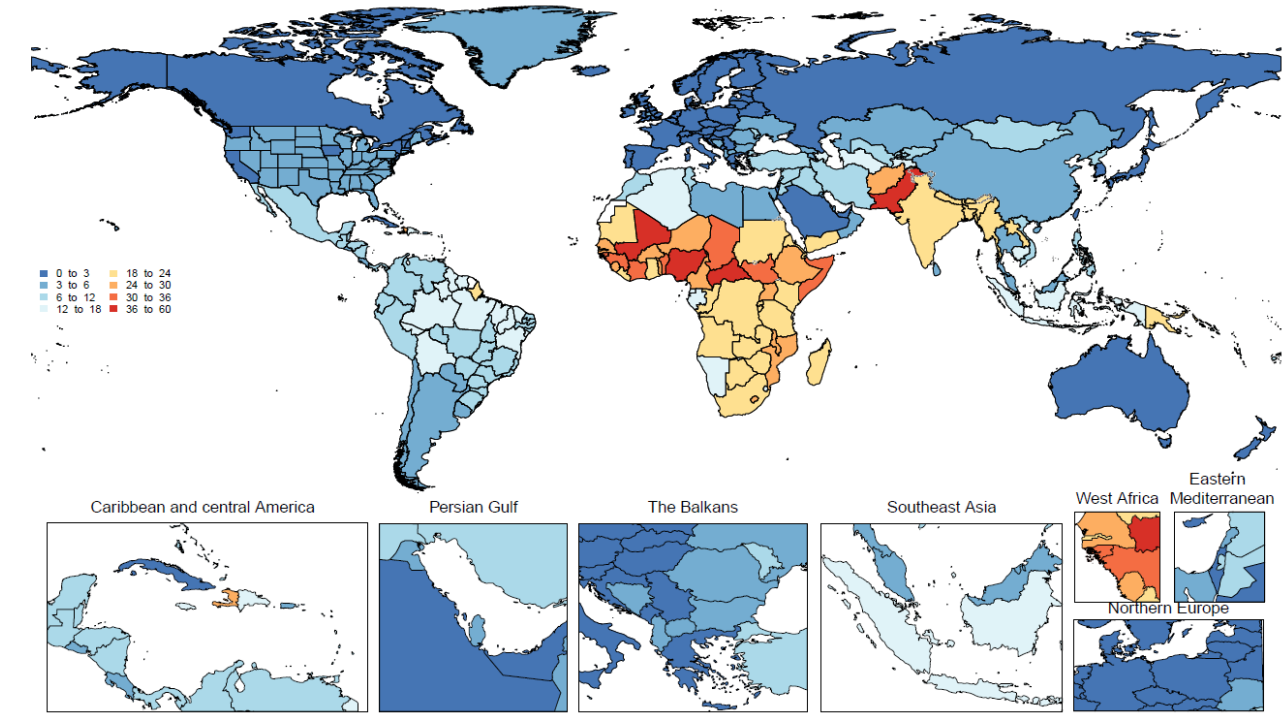


Figure 2 | Neonatal deaths per 1000 livebirths, 2019.
The countries with the lowest NMR were Andorra, Japan, and Singapore. The European Union countries´ lowest NMR was 2 per 1000 livebirths. The ten countries with the highest NMR (in deaths per 1000 livebirths) were Pakistan (42), Central African Republic (39), Somalia (36), Sierra Leone (35), Afghanistan (33), Mali (32), Chad (29), Nigeria (28), South Sudan (28) and Guinea-Bissau (28).
(Image source: Global, regional, and national progress towards Sustainable Development Goal 3.2 for neonatal and child health: all-cause and cause-specific mortality findings from the Global Burden of Disease Study 2019, Lancet 2021 (8), https://doi.org/10.1016/S0140-6736(21)01207-1 licensed under CC BY 4.0)

Concerning the Portuguese reality, in comparison to other Portuguese-speaking African countries (PALOP), NMR has also decreased for these six countries (Chart 1 and Table 1) (10).

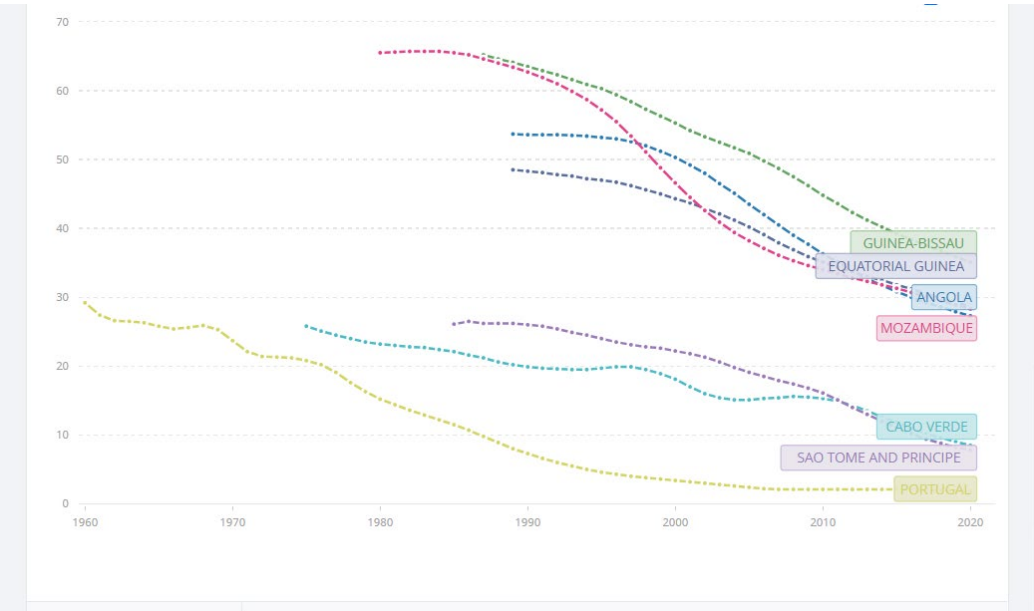


Chart 1 | Neonatal mortality rate (per 1000 livebirths) evolution for Angola, Guinea-Bissau, Equatorial Guinea, Mozambique, Cape Verde, Sao Tome & Principe and Portugal, 1960-2020

(Chart source: UN Inter-agency Group for Child Mortality Estimation. (2023). Neonatal Mortality rate (per 1000 livebirths) for Angola, Guinea-Bissau, Equatorial Guinea, Mozambique, Cape Verde, Sao Tome & Principe and Portugal, 1960-2020. Created using UN Inter-agency Group for Child Mortality Estimation website tools. Retrieved January 10, 2023, from https://childmortality.org/data/Interactive-Chart.)

Although scarce, there are some studies on neonatal mortality and morbidity, from PALOP countries such as Angola (11-14), Mozambique (15-24), Cape Verde (25-27), Guinea-Bissau (28-31) and Equatorial Guinea (32, 33).

Studies on neonatal mortality or morbidity were not found for Sao Tome & Principe.

Table 1 | Neonatal Mortality Rate by Portuguese-speaking African countries compared to Portugal for both sexes combined; in 1990, 2008-2014 and 2020.

		Neonatal Mortality Rate (deaths per 1000 livebirths)		
		1990	2008-2014	2020
HIC	Portugal	**6.9 (6-7.2)***	**2.1 (1.9 – 2.7)**	**1·61 (1·49–1·75)**
LLMIC PALOP	Guinea-Bissau	64 (54-75)	36	31·5 (27·9–35·4)
	Mozambique	63 (56-70)	47 (42-52)	25·8 (21·9–30·7)
	Angola	54 (44-67)	50 (42-61)	21·7 (19·1–24·5)
	Equatorial Guinea	48 (38-63)	44 (36-56)	17·7 (14·8–21·6)
	Sao Tome & Principe	26 (20-30)	22 (17-27)	12·1 (10·2–14·3)
	Cape Verde	20 (17-23)	18 (16-21)	9·46 (8·16–11·0)

Data in parentheses are 95% uncertainty intervals.
Sources: Data for 1990 and 2008-2014 was retrieved from the UN Inter-agency Group for Child Mortality Estimation (10), and data for 2020 was retrieved from the Global Burden of Disease Study, Lancet 2021 (8).

Currently, in the post COVID-19 era, things have probably worsened and the impact on NMR and morbidity is still being evaluated (35). Although COVID-19 infection had a less severe burden on children (2% of global cases and 0.1% of global deaths) (36), it had a huge indirect impact in neonatal morbidity and mortality (37-40). The main indirect impact in neonatal outcomes was associated with lockdowns and restrictions on pregnant women´s access to healthcare services, which led to an increase in low birth weight cases, hypoxic-ischemic encephalopathy, and deaths (35, 37-40).

Additionally, the psychological aspects related to the death of a newborn lead to a very distressing event for the mother and the family, associated with symptoms of maternal depression at a 14-year follow-up (41). Moreover, the total cost of child deaths will also incur a significant loss for the country´s gross domestic product from the future years of life lost (42).

1.2. **When** do newborns die?

Timing and definitions

The critical moments for newborns are birth and the first week of life (2, 4). Three-quarters of neonatal deaths occur during the first week of life, with 25–45% occurring in the first 24 hours (Figure 3) (1, 4).

The cause-of-death distribution differs between the antepartum, intrapartum, early and late neonatal periods (Figure 3) (4, 43). As an example, early neonatal health is inextricably mixed with maternal health, while late neonatal deaths are generally related to neonatal sepsis (43, 44).

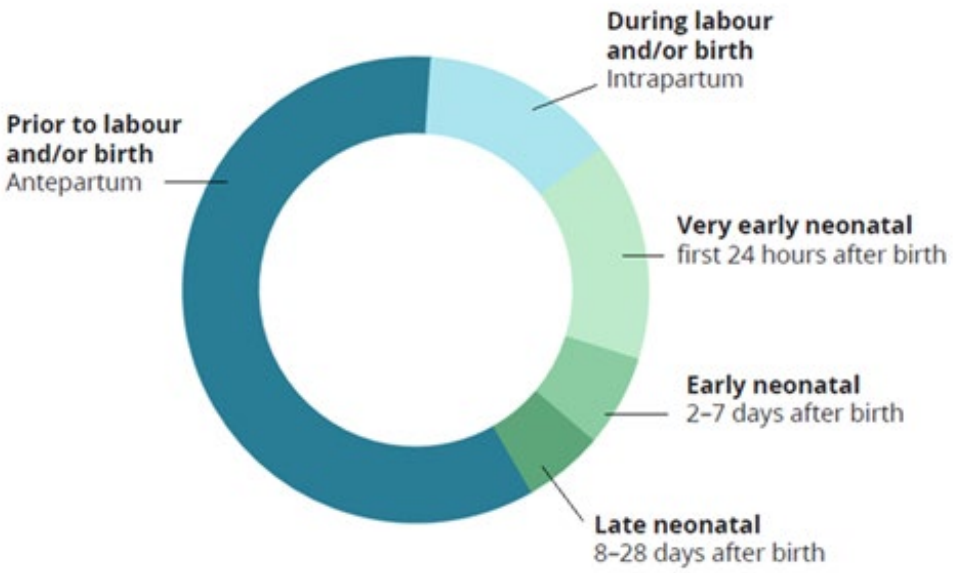


Figure 3 | Timing of perinatal and neonatal mortality. Approximately 75% of deaths occur in the antepartum and intrapartum periods.

(Image source: Australian Institute of Health and Welfare. (2022). Stillbirths and neonatal deaths in Australia. Adapted for a global overview.

Retrieved 10 November 2022 from https://www.aihw.gov.au/reports/mothers-babies/stillbirths-and-neonatal-deaths-in-australia/contents/overview-of-perinatal-deaths)

The overlap of risk factors for each type of perinatal and neonatal death is well recognized, and different adverse birth outcomes can coexist (4, 41, 43). For example, preterm birth, low birth weight, and small for gestational age can exist in a newborn (4, 41, 43).

Factors associated with each condition will be next considered, addressing the main factors known and studied in low-resource countries. The definition, rates, impact, and associated factors for each peri-neonatal death and adverse birth outcome will be considered. Evidence-based cost-effective interventions and main public health measures aimed at reducing and/or preventing each condition will be reviewed in Part II section 3.

1.2.1. Stillbirths

Definition: A stillbirth is a baby born without any signs of life at or after 28 weeks of gestation or at least 1000 g in birth weight (44, 45). They may be classified as intrapartum stillbirths, defined as a dead-born foetus where intrauterine death occurs after the onset of labour and before birth (fresh stillbirth), and antepartum stillbirth, a dead-born foetus where intrauterine death occurs before the onset of labour, designated macerated stillbirth (46, 47).

Rates: Stillbirths dropped from 21.4 per 1000 total births in 2000 to 13.9 in 2019 (46). The global estimate is approximately 2 million stillbirths annually, although there are no high-quality stillbirth data available for 29% of all stillbirths (46). SSA and Southern Asia also bear the greatest burden of stillbirths in the world, although they are often not recorded at all in these settings (44, 46).

Impact: A stillbirth is associated with significant physical, psychosocial, health and economic costs for parents, their families, wider society, and the healthcare system (47). In a subsequent pregnancy, a history of stillbirth is also associated with an increased risk of stillbirth recurrence, antenatal complications, mental health concerns and impact on subsequent children (48). High-impact solutions for stillbirths' prevention and reduction are summarized in Part II section 3.1.

Associated factors: Associated factors for stillbirths are quite different between HICs and LLMICs (49). For instance, in HICs maternal overweight and obesity (body mass index of 25 kg/m2 or higher), maternal age over 35 years, primiparity and smoking are the most important factors (50). In LLMICs, the main factors are those associated with pregnancy complications, such as prolonged pregnancy, maternal infections, such as, malaria, syphilis and HIV, and non-infectious conditions especially hypertension, and diabetes (51-53). In general, other conditions, such as placental abruption, eclampsia, or uterine rupture, can be associated requiring prompt diagnosis and treatment (54). Congenital abnormalities are responsible for less than 10% of stillbirths reported nationally in HICs, but this is not known in LLMICs (50).

1.2.2. Early Neonatal Deaths

Definition: Early neonatal death (ENND), is defined as the death of a newborn between zero and seven days after birth (Figure 3) (55).

Rates: ENND represents 73% of all postnatal deaths worldwide (55).

Impact: Despite a 50% reduction in U5M, the reduction in ENND has significantly lagged behind others, being a growing contributor to overall mortality in children aged less than 5 years (43, 55). High-impact solutions for ENND' prevention and reduction are summarized in Part II section 3.2.

Associated factors: The aetiology is closely related to the level of a country's industrialization (43, 55). For instance, prematurity and congenital anomalies are the leading causes in HICs (55). In low-resource countries, perinatal-related events such as asphyxia and infections together with prematurity are the principal contributors to ENND (56, 57).

1.2.3. Late Neonatal Deaths

Definition: Late neonatal death (LNND) is defined as death after 7 days to 28 completed days of birth (Figure 3) (43).

Rates: Rates for LNNDs are mainly derived from verbal autopsy studies that do not distinguish between sepsis, tetanus, and lower respiratory infections among neonates, given the difficulties in rating LNNDs (3).

Impact: The significant decline in U5M in the last decade can be associated with a reduction in LNNDs (8, 43, 58).

Associated factors: A large multinational study found that sepsis was the major cause of death for late neonatal mortality in low-resource countries (59). Neonatal sepsis will be further discussed in section 1.3.4..

1.2.4. Neonatal near-miss

Definition: Neonatal near-miss (NNM) cases describe situations in which babies are on the verge of dying during the neonatal period due to severe morbidity that occurs during pregnancy, delivery, or extrauterine life but survive either by luck or due to high-quality health care (60).

The 2022 NNM standardized definition is a newborn baby who had at least one of the pragmatic and/or management criteria and survived the first 27 days of life (60). The pragmatic criteria are: 1) birth weight of <1750 grams, 2) an APGAR score of less than 7 at five-minutes of life, and 3) gestational age of <33 weeks (60). The management criteria are one or more of the following events: parenteral therapeutic antibiotics, nasal continuous positive airway pressure, any intubation during the first 27 days of life, phototherapy within the first 24 hours of life, cardiopulmonary resuscitation, vasoactive drugs, anticonvulsants, surfactants, blood products, and steroids for refractory hypoglycaemia, and any surgical procedure, the use of an antenatal steroid, parenteral feeding, congenital deformity, and admission to the neonatal intensive care unit (60). The development of these criteria and the definition of NNM are important for the subsequent creation of an epidemiological surveillance system to be used as a tool for public policy and case management (61).

Rates: Due to the different NNM criteria utilized within every study, the level of NNM differed greatly, estimating that the number of neonates who survived severe morbidities is approximately three to six times higher than those who died (60).

Associated factors: The main associated factors are maternal education, parity, antepartum haemorrhage, hypertensive disorders of pregnancy, history of low birth weight, and frequency of ANC visits, which have all been identified as determinants of NNM in studies conducted around the world (60-63). The associated factors discussed in the following sections can all be related to neonatal near-miss events.

1.3. Why do newborns die?

Focusing on the "why" implies the need to address the main causes of neonatal adverse birth outcomes and mortality (63, 64). In general, neonates predominantly die because they are born too early (premature), too small (low birth weight), or too sick due to intrapartum-related complications (birth asphyxia), birth defects, or/and infections, such as sepsis (Figure 4) (64).

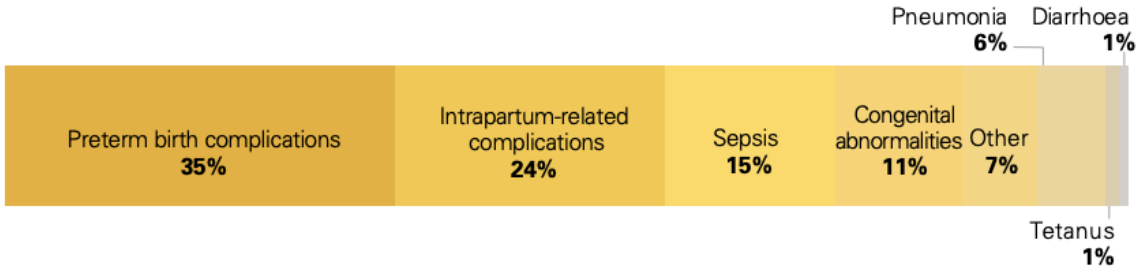


Figure 4 | Global distribution of newborn deaths by cause, 2018. Preterm complications and intrapartum-related complications were related to 59% of overall neonatal deaths.
(Image source: WHO and the Maternal and Child Epidemiology Estimation group. (2018). Global distribution of newborn deaths by cause. Retrieved 1 September 2022 from https://platform.who.int/mortality/themes/theme-details/topics/topic-details/MDB/perinatal-conditions)

Adverse birth outcomes (ABOs), in this thesis, refer to preterm birth, low birth weight, intrapartum birth asphyxia, congenital malformation, and neonatal sepsis and will be next considered for definition, rates, impact and associated factors. Evidence-based cost-effective interventions and main public health measures aimed reducing and/or preventing each condition will be reviewed in Part II section 3.

1.3.1. Born too soon: prematurity

Definition: As previously mentioned, prematurity is defined as being born before 37 weeks gestation (65). There are different cut-offs for premature babies (PTB) based on gestational age: 1) extremely preterm birth - less than 28 weeks, 2) very preterm birth - 28 to 32 weeks and 3) moderate to late preterm birth - 32 to 37 weeks completed weeks or less than 259 days of gestation (66). Ultrasound dating to assess gestational age is not common in SSA countries; therefore, estimation of a low-resource country´s prevalence of PTB and small for gestational age at the population-level is particularly challenging in these contexts (65).

Rates: Globally, 15 million babies are born prematurely each year, and over 60% of them are born in SSA and South Asia (66, 67). The estimated average PTB rate is 12.3% across the SSA region, compared to 9% in HICs (67). Premature-related complications are the world's leading cause of child mortality and 75% of these deaths are estimated to be preventable (68, 69).

Impact: Prematurity has a major impact not only on survival but also on the quality of life for the child, on psychosocial and emotional stress on the family and on costs for health services and society (69). Among children born before 32 weeks who survive, morbidity is particularly high compared to those born at term, as many develop cerebral palsy, and those without severe disability have a twofold or greater increased risk for developmental, cognitive, and behavioural difficulties (65, 69). Moreover, preterm babies often have underdeveloped respiratory systems, with more than 50% of premature babies born before 31 weeks gestation developing respiratory distress syndrome (70). High-impact solutions for PTB prevention and care are summarized in Part II section 3.2. and 3.9.

Associated factors: Factors leading to prematurity are still not completely understood, although the aetiology is thought to be multifactorial (65, 69)**.** There are recognized factors, such as predisposing genetic attributes, advanced maternal age, poor maternal nutrition, preterm premature rupture of the membranes (see section 2.4.2.), a prior history of PTB, vaginal infections and other untreated infections, pregestational hypertension or diabetes, multiparity, multiple births, greater use of assisted reproduction techniques, greater use of elective caesarean section, psychosocial stress, psychiatric disorders, and lifestyle habits such as smoking, alcohol, illicit drug use and exposure to air pollution during pregnancy (41, 69, 71). On the other hand, gynaecological immaturity, defined as a short cervix [≤25 mm] and small uterine volume, increases the risk of preterm delivery among adolescent mothers (72).

1.3.2. Born too small: low birth weight

Definition: LBW babies are defined as a livebirth weighing below 2500 grams (up to and including 2499 g), regardless of their gestational age (73). LBW is further categorized into very low birth weight (VLBW, <1500 g) and extremely low birth weight (ELBW, <1000 g) (73). Low birth weight is a result of preterm birth, intrauterine growth restriction (IUGR, also known as foetal growth restriction), or both (73-75). The birth weight of a newborn is the first weight recorded after birth, ideally measured within the first hours after birth, prior to considerable postnatal weight loss (73, 74).

Rates: LBW infants are a substantial public health problem in every country, and it is estimated that worldwide, more than twenty million infants (representing 15.5% of all births, 95.6% of which occur in resource constrained countries) are born LBW (76). Of the 18 million LBW babies born annually in LMICs, more than 50% do not survive compared to their counterparts born in high-income countries (74).

Impact: LBW is a valuable public health indicator of maternal health, nutrition, healthcare delivery, and poverty (73, 74, 76). They are also at a higher risk of illness shortly after birth and noncommunicable disease in the life course (75). In general, there is a direct relationship between LBW and neonatal mortality, with countries having a high

percentage of children with LBW also having high neonatal mortality rates (74, 76). LBW is also closely associated with increased foetal mortality (stillbirths), low Apgar scores, admission to the neonatal care unit, neonatal morbidity, growth retardation, delayed neurodevelopment, and chronic diseases later in life, such as hypertension (77-79). Moreover, LBW does not differentiate between prematurity and intrauterine growth restriction, and each mechanism may have different long-term effects on schooling and life income (80). High-impact solutions for LBW prevention and care are summarized in Part II section 3.4. and 3.9.

Associated factors: Several studies have reported that maternal characteristics and pregnancy-related events such as maternal age, low pregnancy body mass index, low short maternal stature, low gestational weight, inadequate food intake during pregnancy, vomiting during the early trimester of pregnancy, lack of antenatal care (ANC), antepartum haemorrhage, hypertensive disorders of pregnancy, primiparity, maternal anaemia, malaria during pregnancy, intrauterine growth restriction, congenital malformations and PTB were predictors for low birth weight (74, 75, 77, 78). Epidemiological studies conducted in LLMIC identified some other associated factors for LBW, such as maternal and paternal education and occupational status, and indoor pollution from the type of fuel used for cooking were predictors of LBW (41, 81). Other factors, such as the location of the kitchen in the living house, iron intake less than 180 tablets, and weight gain less than 6.53 kg during the second and third trimester, were also identified as risk factors for low birth weight (75). The high LBW deaths in SSA countries are mainly due to poverty, low socioeconomic status, poor health-seeking and nutrional behaviour, and weak health system links (72).

1.3.3. Intrapartum conditions: foetal distress and birth asphyxia

Definition: Intrapartum conditions refer to the failure to establish breathing at birth (82). Intrapartum asphyxia, in high-income countries, is defined as metabolic acidaemia measured at birth with pH less than 7.00 and base deficit greater than or equal to 12 mmol/l (82). For LLMICs, foetal distress and birth asphyxia are usually defined based

only on the components of the APGAR score table (83, 84), since techniques to evaluate the other parameters, such as umbilical arterial blood gas samples from a clamped section of the umbilical cord, are not available. The score comprised five components: appearance (colour), heart rate, grimaces (reflexes), activity (muscle tone), and respiration evaluated in the first and fifth minutes of life, with scores of zero to ten (84). A score of 0, 1 or 2 is given to each component (84). The definition of foetal distress is a low Apgar score <7 at the first minute of life. The definition of clinical asphyxia is considered in infants with a five-minute Apgar score <7 (84, 85). Assessment of severity and risk for cerebral palsy is considered for an Apgar score of 5 or less at five minutes (84, 85). Lower scores are associated with severe multiorgan damage resulting in brain damage, lung dysfunction, cardiomyopathy, renal failure, hepatic failure, and necrotizing enterocolitis, which are usually applied to both term and preterm infants (86).

Rates: Intrapartum-related complications account for an estimated 900 000 deaths each year and are one of the primary causes of early neonatal mortality (56, 80). Approximately 98% of all asphyxia-related deaths occur during the first week of life, mainly on the first day of life (75%) (86). Furthermore, sequalae are experienced by two million neonates, and 1.2 million have developmental delays (87).

Impact: Intrapartum birth asphyxia complications are associated with hypoxic-ischemic encephalopathy, attention deficit hyperactivity disorder, seizures, and cerebral palsy (86, 87). Birth asphyxia also causes significant financial and emotional burdens on the families and communities involved (80, 82). High-impact solutions for intrapartum birth asphyxia prevention and care are summarized in Part II section 3.5. and 3.9.

Associated factors: The main associated factors can be grouped according to whether they are before, during or after birth (Figure 5) (87-89). The single most important predictor is the quality of intrapartum care during labour, although other factors have been described (87-89). Studies from SSA countries reported other factors, such as night-time delivery and attendance of labour by medical interns alone, to be positively associated with birth asphyxia (88).

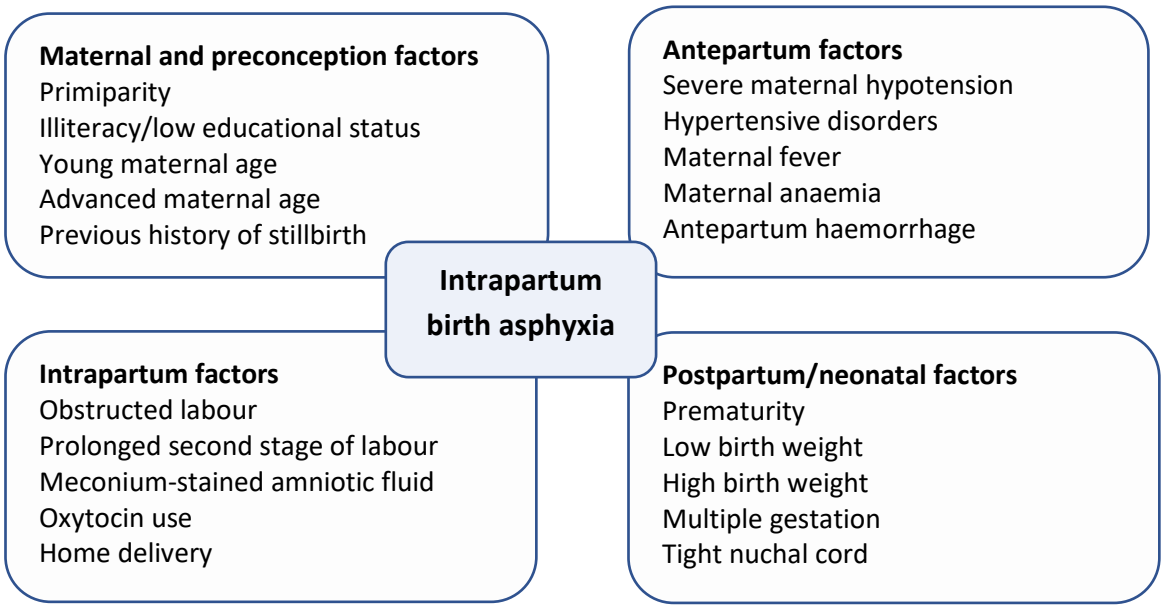


Figure 5 | Main factors associated with intrapartum birth asphyxia.

Source: Schema created by the author with data adapted from references (87-89).

1.3.4. Neonatal sepsis

Definition: Early-onset neonatal sepsis is defined as sepsis occurring in the first seven days of life (preterm neonate in the first 72 hours of life), and late-onset neonatal sepsis, occurs in the following period up to three months of life (90).

History, risk factors and physical examination are the cornerstones of clinical practice, although many challenges are to be considered in this case (90-92). For instance, early signs of infection in neonates are nonspecific and an asymptomatic presentation does not rule out infection (90). Culture confirms the diagnosis and is considered the gold standard, although i) small blood volumes obtained from neonates, ii) the occurrence of low or intermittent bacteraemia, iii) maternal intrapartum antimicrobial administration, and iv) high rates of negative blood culture (80%) can make the confirmation of neonatal sepsis a diagnostic challenge (93). In most SSA countries, only the risk-based diagnosis strategy can be used through the identification of risk factors and timely initiation of antibiotics (92, 93).

Rates: Neonatal sepsis accounts for up to one-third of peri-neonatal deaths worldwide each year (94). In Africa, neonatal sepsis accounts for 28% of neonatal mortality and 68 deaths per 1000 livebirths (94). There is a mostly unquantified burden of short- and long-term morbidity in addition to being a leading cause of peri-neonatal mortality (95).

Impact: Given the circumstances antimicrobial resistance can rise in LLMICs due to unnecessary prolonged empiric antimicrobial therapy (90), owing to the inability to rule out infection due to lack of blood cultures and/or C-reactive protein testing (91).
The spectrum of microorganisms and burden of neonatal infection also varies significantly in HIC and LLMIC settings, with an impact on antibiotic recommendations (96). In most HIC settings, there is a gram-positive (*group B streptococcus* and *Escherichia coli)* predominance while gram-negative bacteria (*Klebsiella pneumoniae)* are likely to cause the majority of early-onset in LLMICs (90, 93). The most common aetiologies (e. g. *group B streptococcus*) will be further discussed in section 2.3. 2. High-impact solutions for neonatal sepsis prevention and care are summarized in Part II section 3.6. and 3.9.

Associated factors: Major diagnostic uncertainty, limits the understanding of its factors in SSA settings (92). The following risk factors were identified for LLMICs in a 2020 systematic review and meta-analysis: 1) prolonged rupture of membrane (PROM) lasting more than 18 hours, 2) urinary tract infection, 3) intrapartum fever, 4) instrumental delivery, 5) prematurity, 6) chorioamnionitis or intraamniotic infection, 7) repeated vaginal examination, 8) never attended antenatal care, 9) home delivery, 10) meconium-stained amniotic fluid, 11) consumption of unclean foods, 12) low birth weight, 13) complicated delivery, 14) low APGAR scores, and 15) invasive procedures during hospital admission (92). Risks factors, such as, clinical chorioamnionitis and PROM are additive (92).

1.3.5. Congenital malformations

Definition: Congenital anomalies/malformations are also known as birth defects and can exist at or before childbirth (97). These malformations can be structural, functional or

metabolic and occur during intrauterine life and can be identified prenatally, at birth, or sometimes may be detected only later in infancy, such as hearing defects (97).

Rates: An estimated 295.000 newborns die within 28 days of birth every year, worldwide due to congenital malformations (97, 98). According to the WHO, 94% of severe congenital anomalies occur in LMICs (97).

Impact: Congenital malformations are also significant causes of chronic illness and disability and translate into an adverse impact on individuals, families, healthcare systems, and societies (99). High-impact solutions for congenital malformations prevention are summarized in Part II section 3.7.

Associated factors: Nearly 50% of all congenital malformations cannot be linked to a specific cause, although there are some known genetic, environmental, and other factors (97-99). For instance, advanced maternal age increases the risk of chromosomal abnormalities (97, 98). Other factors, such as, consanguinity and maternal infections such as syphilis, rubella and Zika are also a significant cause of congenital malformations, esspecially in SSA countries (97, 98). Nutritional risk factors such as maternal folate insufficiency increase the risk of having a baby with a neural tube defect, while excessive vitamin A intake may affect the normal development of an embryo or foetus (97-99).

2. Associated factors

The main factors associated with neonatal deaths and adverse birth outcomes are generally grouped according to whether they are maternal, preconception, occur before birth (antepartum factors), during birth (intrapartum factors), or after birth (postpartum and neonatal factors) (4, 8, 41, 43).

Figure 6 describes the main factors associated with ABOs and perinatal and neonatal deaths according to maternal, preconception, antepartum, intrapartum, and postpartum features.

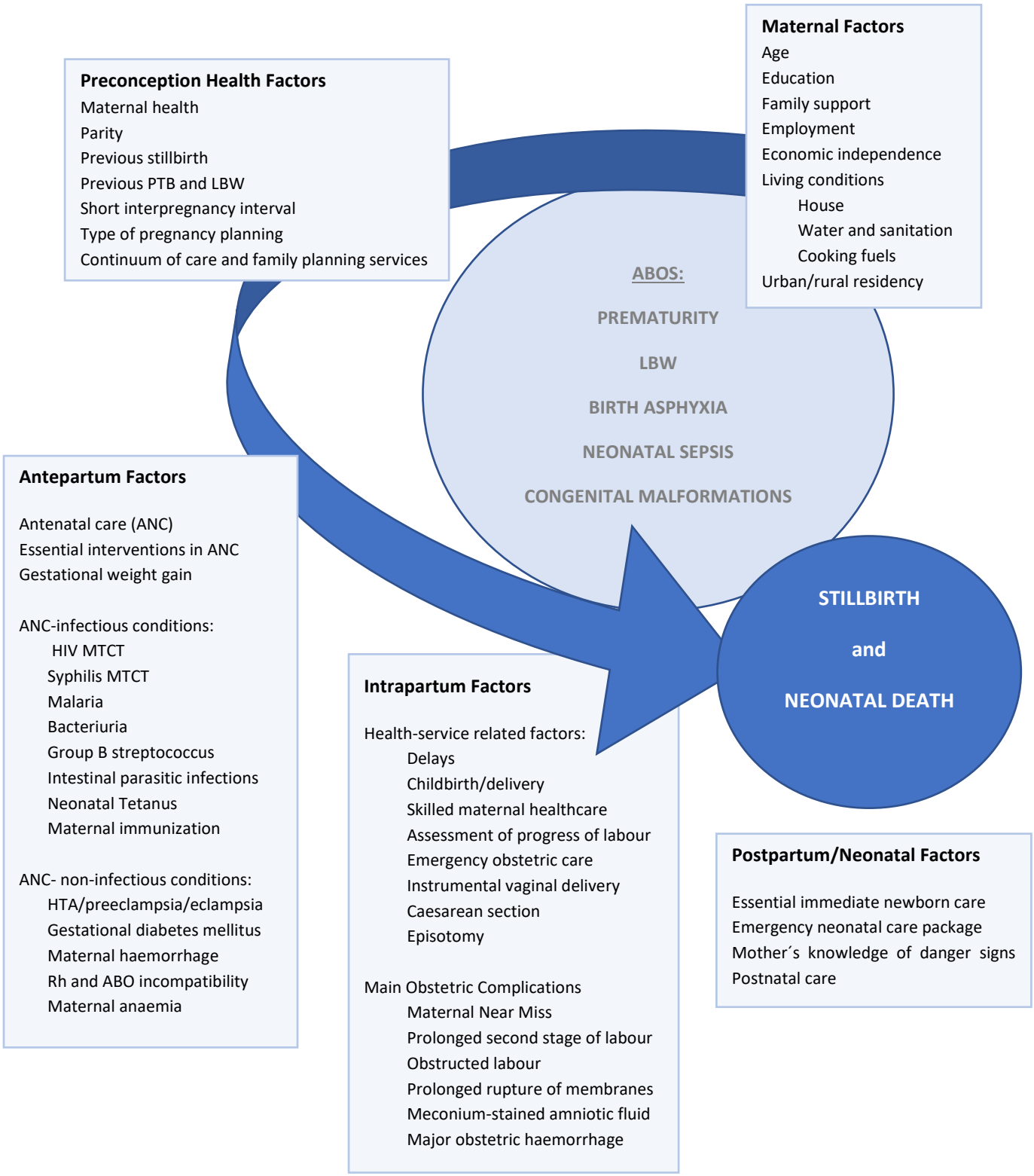


Figure 6 | Main factors associated with adverse birth outcomes, perinatal and neonatal deaths according to maternal, preconception, antepartum, intrapartum, and postpartum features. Schema designed by the author for the main associated factors linked to adverse birth outcomes, perinatal and neonatal mortality.

2.1. Maternal Factors

The health of mothers and of their babies are inextricably bound, and the survival and wellbeing of newborns are compromised by their mother's (72). Pregnancies too early, too frequent, too many and too late, wherever they happen, are associated with an increased risk for neonatal ABOs and death (72, 100). Approximately 20% of diseases amongst babies can be attributed to the mother's poor health status, malnutrition, and inadequate care during the antenatal period (101).

2.1.1. Age: too young and too old

The increased potential for negative pregnancy outcomes in both extremes of reproductive age is well-known (102).

Too young: Adolescent pregnancy is considered the occurrence of pregnancy in girls under or equal to 19 years old and is a major public health problem, particularly in Africa, with an estimated prevalence of 19.3% (103).

Pregnancy and young motherhood are frequently associated with ABOs and are contributors to an intergenerational cycle of poverty (102). There are various factors contributing to it, from biological ones (height and pelvic dimensions only completed by two years after menarche), which might promote cephalopelvic disproportion and consequently to an obstructed labour or other complications, to socioeconomic disadvantages, negative behavioural factors, or a lack of access to high quality antenatal care (101-104).

Teenage mothers can have a higher risk of PTB, LBW, low Apgar score and peri-neonatal mortality (102, 105, 106). Other adverse pregnancy outcomes, such as preeclampsia, caesarean section, vaginal instrumental delivery, and postpartum haemorrhage, are controversial in the literature (72, 100, 101).

Different outcomes can also be associated with younger reproductive ages, such as very young age at first pregnancy (<15 years or so) being associated with an increased risk of maternal anaemia, PTB and LBW than older teenagers (72, 100).

Another important aspect for young girls is child marriage, which occurs often in LLMICs (105). Child marriage, a union occurring before the age of 18, exists in every geographical region and across many cultures and religions (105). Married girls tend to have unintended pregnancies, school dropout and illiteracy, lower labour force participation and earnings, less control over productive household assets, and little decision-making power within the marital home (105).

A meta-analysis identified that in the SSA region, an adolescent was more likely to start childbearing if she lived in a rural area, was married, had lower education, had parents not educated, or lacked parent-to-child communication on sexual and reproductive issues (107). Poor reproductive health services provision and inadequate attitude of health workers to provide contraceptive services for adolescents are also main barrier factors referred to in the literature for low resource settings (101, 103, 104, 107). High-impact solutions for adolescent pregnancy prevention are summarized in Part II section 3.11.

Too old: Women above the age of 35 years have traditionally been termed "elderly pregnant women" (108). Adverse birth outcomes (foetal distress, birth asphyxia, LBW, and PTB) and obstetric complications (caesarean section) generally increase with age (102). At older maternal ages, the cooccurrence of chronic diseases with pregnancy and other diseases is cumulative, and genetic defects become more common, all leading to spontaneous abortions and peri-neonatal deaths (109). Again, some studies fail to demonstrate such unfavourable conclusions (102). There are alternative arguments supporting that the social and economic advantages of older women outweigh biological vulnerability, but this still needs to be proven (102).

2.1.2. Education

The effect of education is widely known and empowers women to make healthy choices about their own and their children's lives (4, 72, 100). Educated mothers have better access to information, have an enhanced position in the household that allows them to have decision-making power about health-related choices, use reproductive health services, and prevent unintended pregnancy (110). Women who are less educated have more children, on average five to six children, than more educated women (on average 1.7 children) (55, 110). Currently, two-thirds of the illiterate people in the world are

women, and 53% of the world's out-of-school children are girls (110). Especially in SSA countries, since girls graduated from primary school, one-quarter to one-half cannot read a single sentence (110).

2.1.3. Family support

The definition of family can mean and assume distinct concepts according to different regions in the world (111). In high-income countries, society marriage represents the basis of the family, defending a more individualistic and independent character (112). In contrast, in SSA societies, the focus is on the community, and the concept of family is therefore extended, based on the principle of collectivity and interdependence (111).

Family support is clearly important to pregnant women and to the baby, with maternal grandmothers appearing to have a positive influence on parenting behaviour and practices, mainly at younger ages (112). Partner/paternal support is linked with improved financial and psychological/emotional outcomes (111). Peers also appear to play an important role in emotionally supporting the teenage mother, although there is much less research on this support (112).

2.1.4. Employment and economic independence

Currently, women arguably have the greatest opportunities of any past generation to have economic independence and power to make choices (113). In a well-functioning society, women should be afforded a job, that is not yet a given in some societies, mainly in the SSA region, which can lead to worse health outcomes (114). Unemployment, economic dependency, and poverty are linked and increase disease risk due to poor housing, water, sanitation and hygiene, and adverse nutrition behaviours, such as, poor dietary practices and food insecurity (115).

Moreover, in the SSA region, pregnant women are susceptible to inadequate access to anaemia prevention and treatment services such as iron supplements, deworming and insecticide-treated bed nets (4, 8, 41, 101, 115).

2.1.5. Living conditions

House: A potential contributor to adverse birth outcomes is inadequate housing and poor living conditions, a modifiable exposure (116). Studies have linked poor housing

conditions, mainly crowding, inadequate sanitation, and construction materials, to adverse birth outcomes such as premature birth and low birth weight (116).

Water supply, sanitation, and hygiene: Recognized as the "forgotten foundations of health", water supply, sanitation, and hygiene (WASH) has been one of the greatest medical advances since 1840 (117). Globally, 82% of the urban population uses improved sanitation facilities, compared with 51% of the rural population (118). Nonetheless, globally, inadequate WASH is still a major contributor to the overall mortality and burden of disease (119). Lack of WASH is responsible for diarrhoea-causing infections and is also indirectly associated with trachoma, acute respiratory tract infections, and undernutrition in children (117, 119). Regarding adverse birth outcomes, a prospective study reported that women with poor sanitation practices in the early phase of pregnancy were more likely to experience an adverse outcome (120). Open defecation was also significantly associated with increased odds of preterm birth (AOR 2.22; 95% CI: 1.29–3.79) but not low birth weight (AOR 1.61; 95% CI: 0.94–2.73) (120).

Cooking fuels: Approximately 3.8 billion people in LMICs use unclean fuel for cooking (121). Many individuals from SSA countries, especially women, still use the combustion of highly polluting unclean fuels (coal, charcoal, wood, dung, kerosene) during cooking (121). Regarding ABOs, Younger et al. reported an increased risk of LBW, PTB, small for gestational age, stillbirth, and neonatal mortality with solid fuel and kerosene use compared to cleaner fuels (121). Another study found that cooking fuels, namely, firewood and kerosene, had a risk for LBW and that having a kitchen in the same living house (proxy of indoor air pollution) had a 2.5 times higher risk of delivering a LWB (75).

Climatic conditions: Interestingly, there seems to be a relationship between climate exposure variables and some pregnancy outcomes, including eclampsia, preeclampsia, LBW, PTB, hypertension, sex ratio and length of pregnancy (122). According to some authors, a decrease in birth weight is more likely to occur in cold months, and preeclampsia/eclampsia is more likely to occur in humid seasons (122). A correlation between the increase in temperature, heat, and sunlight was also associated with higher rates of PTB and hypertension, and preeclampsia/eclampsia (122, 123).

Exposure to PM2.5 (fine particulate matter that is less than or equal to 2.5 micrometers in diameter) during pregnancy has also been linked to adverse birth outcomes, mainly in

South Asia and sub-Saharan Africa, where the highest levels of PM2.5 are found (124). It is estimated that exposure to PM2.5 contributes to approximately 17% of the global burden of neonatal disorders and is associated with stillbirths, PTB, LBW, and neonatal mortality (124).

2.1.6. Urban and rural residency

Pregnant women living in rural communities can be subject to a higher degree of risks, for example, 1) environmental exposure to potential sources of infection through contaminated water, farm animals and wildlife, 2) poorer hygiene practices and sanitation, 3) fewer health-seeking behaviours and lack of awareness of pregnancy and neonatal danger signs, and 4) inadequate accessibility to health services with high costs for transportation (54, 61, 109).

Poor access to local health facilities and a lack of road infrastructure or transportation causes women, mainly in the SSA region, to travel long distances on foot, resulting in delays in accessing health facilities, which might lead to maternal near-miss events and risk for ABOs and peri-neonatal mortality (109). For example, in Guinea-Bissau, a six-year longitudinal population-based study identified that women living 6–25 km from a hospital had a higher risk of dying from a pregnancy-related complication than those living 0 to 5 km from a hospital (54). Two other studies from Ethiopia reported a higher rate of ABOs among newborns whose mothers had a rural residency (61).

2.2. Preconception Health Factors

2.2.1. Maternal health

Maternal chronic diseases, such as diabetes, hypertension, asthma, epilepsy, and depression are well-known risk factors for ABOs (109, 125). One study found that the odds of having ABOs were two times higher among women with preexisting medical disorders (126). Studies in SSA countries, such as Nigeria, Ghana, Sudan, and Ethiopia, have also recognized that a history of maternal anaemia and chronic hypertension resulted in a maternal near-miss and ABOs (109). Moreover, the likelihood of complications such

as superimposed preeclampsia, placental abruption, intrauterine growth retardation, and preterm delivery is substantially enhanced by those chronic conditions (109).

2.2.2. Obstetric history

Obstetric history is associated with birth outcomes, and it is a factor used to define high-risk pregnancies (127).

Primigravidae and nulliparae: Primigravidae and nulliparae are obstetric high-risk groups, especially very young and elderly pregnant women. Primigravidae have been found to be associated with anaemia, pregnancy-induced hypertension, preeclampsia/eclampsia, preterm labour, and malpresentation (128). Compared with multiparous women, nulliparae are more likely to have labour complications that require intervention because more uterine force is needed to overcome the resistance in the reproductive tract, and the uterus tends to be less active in preserving uterine contractions (128). The foregoing may elucidate why dystocia occurs, with 50% of all caesarean deliveries in nulliparae being related to dystocia (128). Furthermore, labour induced with oxytocin and assisted vaginal deliveries are most common in nulliparae (128).

Grand multiparity: Grand multiparity is defined as women with a parity of five or more, or as referred by Solomon in 1934, as “the dangerous multiparas”, because the threshold of risks increases markedly at parity ≥5 (129). There is an estimated 3–4% prevalence of grand multiparity in SSA countries as a result of limited access to contraceptives and family planning services (129). Maternal complications are mainly hypertension, anaemia, antepartum haemorrhage, abnormal foetal presentation, postpartum haemorrhage, and dystocia (129, 130). Additionally, it is also linked to LBW, PTB, and congenital malformations (130). Pregnant women with high parity usually have a low literacy and poverty and are subject to other forms of injustice and inequity (130). In the SSA context, the desire for large family size, the longing to have a child for a new husband, gender preferences, loss of a child and failed contraception result in a higher number of pregnancies (130).

Previous history of abortion: A previous abortion can be linked to ABOs in an upcoming pregnancy due to short- and long-term consequences of abortions, such as cervical insufficiency and uterine adhesions (61). Studies have shown that spontaneous miscarriage increases the risk of ABOs in a future pregnancy, such as, a low Apgar score at first minute, low birth weight and intrauterine growth restriction. Abortions can also be associated with genetic, immunological, infectious, or uterine abnormalities with an impact on subsequent pregnancies (61). Furthermore, as the number of abortions increases, the magnitude of the estimated ABOs also increases (61).

Previous history of stillbirth: Neonates whose mother had a previous stillbirth are at higher risk of experiencing ABOs (131). A 2021 study in Ethiopia reported that the odds of neonatal near miss were 4.8 times higher among mothers who had a previous stillbirth (61), consistent with the findings from another study conducted in Bangladesh (132).

Previous history of a preterm and/or low birth weight baby: The recurrence risk of a premature baby is estimated to range from 16% to 30.2% (48, 127). Mothers who had a history of delivering very low birth weight babies (less than 1500 g) are also more likely to have subsequent LBW (127). A study conducted in Ethiopia found that a previous history of child-related ABO had a fourfold higher risk for a new ABO (AOR 4.1, 95% CI:2.5–6.8) than not having a previous PTB or LBW (41).

Short interpregnancy interval: Interpregnancy intervals shorter than 6 months increase the risk of PTB by 1.40 times and LBW by 1.61 times (79) and are also a risk factor for maternal and/or neonatal death (133). Short interpregnancy intervals or closely-spaced second pregnancies are associated with poor maternal nutritional status and folate depletion, cervical insufficiency, premature membrane rupture, abruptio placentae and placentae praevia, uterine rupture among women with previous caesarean section, incomplete healing of the uterus, abnormal remodelling of endometrial blood vessels, infections, suboptimal lactation for the newborn, and sibling competition (109, 133, 134). Therefore, the WHO recommends an interval between the last livebirth and the next pregnancy of at least 24 months, meaning a birth interval of 33 months (133).

Unplanned pregnancy: A pregnancy that is unplanned is associated with a higher probability for the women not to pay enough attention to their pregnancy or receive essential information such as dietary counselling and foetal monitoring (101). This exposes the foetus to a variety of problems that later develop into ABOs and near-miss events (109). Unplanned pregnancies are mainly the rule in SSA countries, as women are less likely to access reproductive services in many contexts, mainly due to ignorance and lack of modern contraception (41, 50, 55, 127).

2.2.3. Continuum of care, reproductive and family planning services

Reproductive and family planning services are essential components of comprehensive reproductive healthcare (101). There are two important core dimensions for the continuum of care: sequential time and space (101, 127, 135). The time dimension consists of service delivery from pre-pregnancy to childhood, while the space dimension involves community–family care, outreach–outpatient care, and clinical care (101). The frequency and timing of care delivery are important considerations in defining the continuum of care (101). A systematic review and meta-analysis found that continuum of care (linking pre-pregnancy and pregnancy care) was effective in reducing ABOs (risk ratio [RR]: 0.79; 95% CI: 0.71–0.89, I 2 = 62%) and perinatal mortality (RR: 0.84; 95% CI: 0.75–0.94, I 2 = 73%) (101). This is related to the previously discussed that too early, too many and too close births, and previous stillbirths, PTB and LBW are linked to neonatal adverse outcomes or their recurrence (136). Another important aspect is women's poor knowledge of preconception healthcare, since those with poor knowledge are more likely to have an ABO (AOR 3.0, 95% CI: 1.4–6.6) than those who had good knowledge (135). Lack of family planning services was also associated with a five times higher risk of experiencing ABOs in a study from a SSA setting (136). Currently, in most SSA settings, maternal health care does not start until the pregnancy is well established and not until more than half of the pregnancy has passed (135). High-impact solutions for enhancing continuum of care care are summarized in Part II section 3.10.

2.3. Antepartum Factors

2.3.1. Antenatal care

Current antenatal care (ANC) programmes have grown from models developed in Europe in the early decades of the past century (137). The concept began from the rising belief at that time that avoidance of maternal death as well as infant death was possible (138).
Over the past decades, a variety of ANC models proposed by the WHO have been implemented in LLMICs (137, 138). One such model was the Focused Antenatal Care (FANC) programme, implemented between 2001 and 2016, with a total of four ANC visits for noncomplicated pregnancies (138). Recently, in 2016, the WHO released a new guideline recommending a minimum of eight ANC contacts to reduce perinatal mortality and improve mothers' experience of care (139). The now use term is "contact", replacing the term "visit", as it implies an active connection between a pregnant woman and a health-care provider (139).
Studies in ANC services in Africa are still focused only on coverage as a dose-response effect, as antenatal care programmes often seek to increase the quantity of attendances provided without considering the quality (17, 109, 138).

Essential ANC screenings include the identification and management of frequent antenatal problems and obstetric complications, aimed at reducing ABOs and mortality (139). ANC screenings can be classified according to their purpose into detecting/preventing non-infectious conditions or infectious conditions. Antenatal screenings of infectious conditions are mainly aimed at diagnosing those associated with mother-to-child transmission (MTCT), namely, HIV, syphilis, and hepatitis B virus, or that impact neonatal outcomes, such as malaria, tuberculosis, asymptomatic bacteriuria and intestinal parasitic infection (139).

The WHO package of main interventions and screenings for ANC in SSA countries includes the following: 1) daily oral iron and folic acid supplementation with 30 mg to 60 mg of elemental iron and 400 g (0.4 mg) of folic acid; 2) full blood count testing (where it is not available, on-site haemoglobin testing with a haemoglobinometer is

recommended for diagnosing anaemia in pregnancy); 3) midstream urine culture (most frequently, dipstick tests are the only method available in resource-constrained settings); 4) blood glucose testing; 5) provider-initiated testing and counselling for human immunodeficiency virus (HIV), syphilis and HBV; and 6) an early ultrasound before 24 weeks of gestation (139).
Core elimination of MTCT for LLMICs includes primary prevention of HIV, syphilis, and HBV among women of childbearing age; antenatal screening for HIV, syphilis, and HBV; prompt linkage to care for pregnant women who test positive; safe delivery; treatment and follow up of exposed infants; and optimal infant-feeding (140).

Strategies aimed at preventing each ANC problem will be briefly addressed next.

2.3.2. Antenatal problems | infectious conditions

Intrauterine infections, which are more frequent in SSA countries, are associated with peri-neonatal deaths and adverse outcomes with various short- and long-term effects on child health and development (50, 94, 141).
Active TB infection during pregnancy increases the risks of PTB and LBW babies (94, 141). Another burden in the SSA region is malaria, which is also strongly associated with PTB and LBW due to placental infection (94, 141).
Often, the consequences of these infections are dependent upon the timing of foetal exposure to the microorganism in question (41, 141).

Mother-to-child transmission of HIV: MTCT of HIV accounts for approximately 9% of new HIV infections, with 160.000 children newly infected in 2018 (140). Infection with HIV occurs during pregnancy or childbirth (15-30%) and through breastfeeding (36.4%) if the pregnant women do not receive treatment during pregnancy (142). MTCT of HIV has been almost completely eliminated in HICs (140, 143). In 2015, Cuba became the first country in the world to be validated for having achieved elimination of MTCT of HIV and syphilis (140). Meanwhile, another 15 countries received the WHO validation

as EMTCT of HIV and/or syphilis, showing that this is possible through pregnancy surveillance (140).

Mother-to-child transmission of syphilis: Congenital syphilis is the second leading cause of preventable stillbirth globally, preceded only by malaria (144). Syphilis during pregnancy can lead to adverse foetal outcomes in the second or third trimester, including early foetal death, stillbirth, neonatal death, PTB, LBW and congenital infection and deformities in newborns (144, 145).
Globally, the burden of congenital syphilis decreased between 2012 and 2016, from approximately 750.000 to 660.000 cases of congenital syphilis (145). Preventing MTCT of syphilis through expanded early testing in ANC and immediate treatment with a single injection of benzathine penicillin is highly cost-effective since the risk of adverse outcomes to the foetus is minimal with adequate treatment early in pregnancy – ideally before the second trimester (144, 145).

Mother-to-child transmission of HBV: Chronic HBV infection is an important cause of morbidity and mortality, mainly among pregnant women (140). Most of the disease burden of HBV results from infections acquired in infancy through perinatal or early childhood exposure to HBV (140). Globally, it is estimated that 296 million people are living with chronic HBV infection, with 1.5 million new infections occurring each year (140). The triple elimination of MTCT (EMTCT) of HIV, syphilis and HBV has been identified by the WHO as a global public health priority (140).

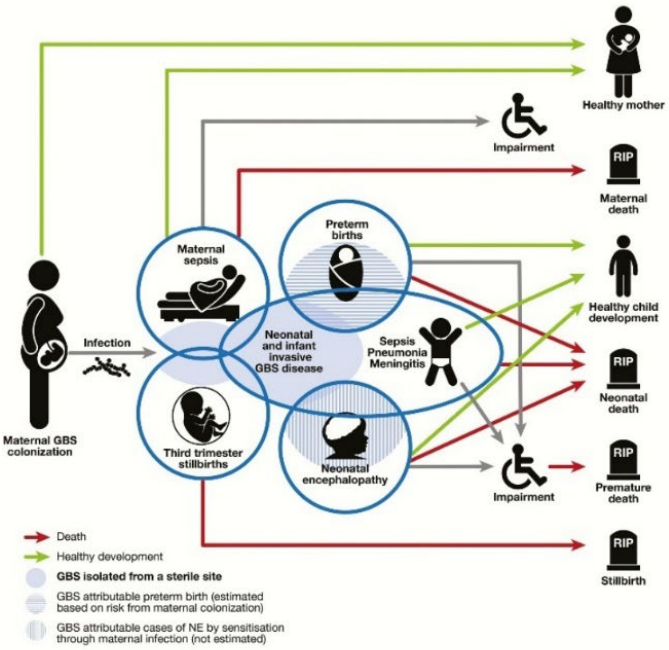
Malaria: Malaria infection during pregnancy is a major public health problem in SSA, with the WHO African Region accounting for 95% of all cases in 2020 (146). It is estimated that *P. falciparum* causes 50 000 maternal deaths and 200 000 stillbirths each year (147).
Malaria is also known to cause higher rates of miscarriage, prematurity, LBW, and neonatal deaths (148). Currently, the WHO recommends the administration of intermittent preventive treatment in pregnancy with sulfadoxine-pirymethamine (IPTp-SP) at each scheduled ANC visit for all women living in moderate to high transmission areas (139, 146). The goal is to ensure the administration of at least three doses of SP

during pregnancy, starting in the second trimester of gestation, with doses administered at least one month apart (146). Each dose of IPTp-SP consists of three tablets, irrespective of the presence of parasites, under directly observed therapy (DOT) and has been proven to reduce maternal and placental infection, protect against maternal and foetal anaemia, and reduce the rates of maternal and foetal mortality (146-148).

Asymptomatic bacteriuria in pregnancy: Asymptomatic bacteriuria in pregnancy, if untreated, is associated with a 30–40% incidence of maternal pyelonephritis and cystitis and newborn adverse outcomes such as PTB and LBW (149). Asymptomatic bacteriuria is a common urinary tract condition because of the many changes associated with pregnancy from anatomic and physiological to reduction in immunity, decreased urine volume and gestational-induced glycosuria that create an environment for bacterial proliferation (149). Symptomatic bacteriuria poses fewer problems because of its easy diagnosis and treatment due to its overt symptoms (149, 150).
Aetiology is diverse, showing the geographical variability of causative agents. Globally, *Escherichia coli* is associated with up to 80% of isolates; other pathogens include Klebsiella species, Proteus mirabilis and *group B streptococcus* (149, 150). Therefore, to prevent untoward complications, it should be mandatory to perform routine urine screening for all pregnant women attending ANC even in the absence of symptoms (139). The gold standard method is to perform a midstream urine culture (139). In most SSA countries, there is no means to perform urine culture techniques, so the frequently used method is a urine dipstick to test for nitrites and leucocytes, to identify the presence of bacteria and pus in the urine (139). According to WHO recommendations, a seven-day antibiotic regimen is recommended for all pregnant women with bacteriuria to prevent persistent bacteriuria, PTB and LBW (139).

Infection with *group B streptococcus:* In SSA countries, *group B streptococcus* (GBS) continues to cause significant morbidity and mortality (Figure 7), although in most areas, data on maternal colonization, vertical transmission and neonatal GBS infection remain scarce (151, 152). GBS is a frequent cause of a wide range of adverse outcomes (Figure 7), for example, ASB, urinary tract infection, upper genital tract infection (i.e., intra-amniotic infection or chorioamnionitis), post caesarean wound infection, postpartum

endometritis, pneumonia, puerperal sepsis, and bacteraemia without a focus (153). It can also cause focal neonatal infections, such as meningitis and endocarditis, although rarely (94, 153). The risk of neonatal infection following maternal colonization can be up to 9.4 times higher for colonized mothers than for noncolonized mothers (94, 151). A recent meta-analysis provided estimates of GBS maternal colonization of 22.4% in Africa, 19.7% in the Americas, and 11.1% in Southeast Asia (94). One study in Ethiopia reported a 45% transmission rate based on maternal and neonatal swabs, with more than 65% of pregnant women not receiving intrapartum antibiotics (151).



Parameter	Case definitions used for estimates	Estimate
Group B *Streptococcus* maternal colonization	Isolation by culture of GBS from either the vagina (high or low), rectum or peri-anal region at any time during pregnancy	**21,734,000** (16,034,000-27,764,000) live births exposed
Maternal GBS disease	Laboratory isolation of GBS from sterile site in pregnant or postpartum woman (up to 42 days postpartum), with clinical signs of sepsis	**33,000** (13,000-52,000)
Stillbirth GBS invasive disease	Birth of a fetus weighting >1000g and/or ≥28 weeks' gestation age with no signs of life and evidence of GBS invasive disease from a normally sterile site such as fetal blood, lung aspirate or cerebrospinal fluid	**57,000** (12,000-104,000)
Neonatal and infant GBS invasive disease	Laboratory isolation of Streptococcus agalactiae from a normally sterile site in an infant aged 0 to 89 days with signs of clinical disease, including meningitis, sepsis or bacteremic pneumonia	**319,000** (119,000-417,000)
Neonatal encephalopathy with invasive GBS disease	Laboratory isolation of GBS from a sterile site (blood, cerebrospinal fluid analysis or on a post mortem sample) in cases of neonatal encephalopathy, hypoxic-ischaemic encephalopathy and intrapartum-related death	**7,000** (300-19,000) as a subset of all invasive disease cases
Neurodevelopment impairment in children after GBS invasive disease	Cognitive and/or motor, vision or hearing impairment in survivors of invasive infant GBS disease isolated from a normally sterile site	**10,000** (3,000-27,000) cases after GBS meningitis. Unable to estimate for sepsis
Preterm birth associated with GBS maternal colonization	Delivery prior to completion of 37 weeks' gestation from mother with maternal GBS colonization isolated from vaginal, cervical and/or rectal swabs	**Up to 3.5 million**

Figure 7 | Outcomes of maternal group B *Streptococcus* colonization displaying worldwide estimates for 2015. Original image adapted from Lawn et al (154). Abbreviations: GBS, group B Streptococcus; NE, neonatal encephalopathy.

(Image source: Estimates of the Burden of Group B Streptococcal Disease Worldwide for Pregnant Women, Stillbirths, and Children, Clinical Infectious Diseases 2017 (152), https://doi.org/10.1093/cid/cix664 licensed under CC BY 4.0)

TORCH infection: Other maternal infections, including 'TORCH' pathogens (Toxoplasma gondii, 'other' infections, rubella, cytomegalovirus, and herpes simplex), are responsible for a range of foetal malformations and defects that vary from somewhat mild to severely debilitating (141). Other organisms included in the TORCH pathogens are parvovirus, human immunodeficiency virus, Epstein – Barr virus, herpes viruses 6 and 8, varicella, syphilis, enteroviruses, and hepatitis (155). In general, these intrauterine infections are associated with a higher rate of miscarriage, congenital anomalies, microcephaly, intracranial calcifications, intellectual disability, vision and hearing impairment, and a group of other systemic findings specific to the particular infection (141, 155).

Intestinal parasitic infections: Intestinal parasitic infections (IPIs) affect millions of pregnant women worldwide, with a high prevalence (24 to 70%) in endemic settings (156). IPIs can lead directly and indirectly to a spectrum of adverse maternal and foetal/placental effects and are a major cause of maternal anaemia and ABOs (139, 156, 157). Infection is often more severe in primigravida and is likely to have a higher degree of parasitaemia (156). Moreover, as enteric nematodes, cestodes, trematodes and protozoans often occur simultaneously in endemic areas, polyparasitism has been suggested to have a synergistic effect in exacerbating detrimental health outcomes in infected pregnant women (157, 158). This is the main factor that causes or aggravates preexisting maternal anaemia, and leads to deficiencies of iron, protein, folate, and zinc, resulting in low pregnancy weight gain, intrauterine growth retardation, low birth weight, greater risks of infection, and higher perinatal mortality rates. (156, 157). The WHO current recommendations for the SSA region for soil-transmitted helminths (STHs) in endemic areas (with a 20% baseline prevalence of hookworm and/or *T. trichiura* infection and a 40% prevalence of anaemia among pregnant women), namely, Angola, Burkina Faso, Cameroon, Ethiopia, Ghana, Kenya, Mozambique, Nigeria, Rwanda, and Uganda, are deworming with a single dose of albendazole (400 mg) or mebendazole (500 mg) after the first trimester (139, 159). Praziquantel for schistosomiasis can be administered at any stage of pregnancy and during lactation (159). For STH high-risk countries with a prevalence ≥50%, for example, Democratic Republic of the Congo, Burundi, Guinea,

Mali, Niger, Sierra Leone and Tanzania, the WHO recommends one or two treatments per year, respectively (139).

For nonendemic areas, infected pregnant women should be treated in the second or third trimester on a case-by-case basis (139). The major obstacle to routine anthelminthic preventive chemotherapy in pregnancy in these endemic countries is the concern that the drugs may have teratogenic effects on the foetus, as well as a lack of evidence supporting the health benefits on maternal and neonatal outcomes of treatment during pregnancy (160, 161).

Tetanus: Tetanus is an acute disease caused by an exotoxin produced by *Clostridium tetani* (162). In many countries, deliveries take place in unhygienic circumstances, putting mothers and their newborn babies at risk of a variety of life-threatening infections, namely, neonatal tetanus (162). This neonatal disease occurs within the first two weeks of life and causes generalized rigidity and painful muscle spasms, which in the absence of medical treatment lead to death (139). As tetanus spores are ubiquitous in the environment, eradication is not biologically feasible; unlike polio and smallpox, tetanus cannot be eradicated, but through immunization of children, mothers, other women of reproductive age and promotion of more hygienic deliveries and cord care practices it can be eliminated (as few as one case of neonatal tetanus per 1000 livebirths in every district) (162). The most important elimination strategy is to achieve ≥80% coverage with ≥2 doses of tetanus toxoid-containing vaccine among women of reproductive age through routine immunization of pregnant women, followed by skilled birth attendant care at ≥70% of deliveries (163).

Maternal immunizations: ANC immunizations provide a first window of opportunity to protect neonates against deadly pathogens such as tetanus, diphtheria, pertussis, and influenza through the transfer of antibodies from the mother to the foetus via the placenta (163). Recommended vaccines for a pregnant woman that has not previously been vaccinated, or if her immunization status is unknown, is to give two doses of a tetanus toxoid-containing vaccine (TT-CV) one month apart with the second dose offered at least two weeks before delivery (163). One to three years of protection is usually achieved after two TT-CV doses (163). The total of five doses protects throughout the childbearing years

(139, 163). The global vaccination programme against tetanus has reduced an estimated 146 000 neonatal tetanus deaths in 2000 to 25 000 neonatal tetanus deaths in 2018, meaning an 88% reduction (163). By 2018, elimination had been validated by the WHO in 45 (76%) of the 59 priority countries (163). While progress continues to be made, by March 2022, 12 countries have still not reached the Maternal and Neonatal Tetanus Elimination Initiative, namely, Afghanistan, Angola, Central African Republic, Guinea, Mali, Nigeria, Pakistan, Papua New Guinea, Somalia, Sudan, South Sudan, and Yemen (162).

Other vaccines, such as those against rubella and pertussis, are routinely administered in pregnant women in many HICs, but not in most LMICs (100, 139). The uptake of maternal vaccines remains an ongoing challenge in LMICs, despite proven benefits, in part due to limited access of these women to ANC services or cultural beliefs (100, 139). Increasing consideration should also be given to developing safe, effective vaccines against respiratory syncytial virus infection and *group B streptococcus* since these infections remain a major source of morbidity and mortality in LMICs (94). Recently, promises for a vaccine that protects pregnant women from malaria can be a huge change for ABOs and peri-neonatal mortality in endemic countries (147).

2.3.3. Antenatal problems | noninfectious conditions

Poor gestational weight gain: Gestational weight gain is a key mediator of birth outcomes, and a strong risk factor for other pregnancy complications on its own (164). Maternal diet is a modifiable risk factor and a poor diet may result in poor maternal nutrition status and adverse outcomes, including LBW, PTB, IUGR, and neural tube defects (164, 165).

The minimum standard gestational weight gain during the second and third trimester is set as 6.53 kg, since it has been shown that women who gained less than 6.53 kg had a higher risk of delivering LBW babies with reference to women whose weight gain was 6.53 kg or above (AOR 2.8, CI: 1.6–5.0) (75). Higher-quality maternal diets (consumers of dairy, fruits, and dark green leafy vegetables) were associated with lower risks of inappropriate gestational weight gain, LBW and PTB (164).

Anaemia: Maternal anaemia is defined as a blood haemoglobin (Hb) concentration less than 11 g/dL (139). Globally, maternal anaemia is estimated to affect 38.2% pregnant women. HICs have a lower rate of 25.8% in Europe and 5% in the United States of America, compared to the highest prevalence of 48.7% in Southeast Asia and 46.3% in Africa (166). Anaemic pregnant women have a 30% to 45% chance of having ABOs, and their infants have less than one-half of normal iron reserves (158, 166). Iron deficiency adversely impacts cognitive performance and development as well as the physical growth of these babies (159). Studies estimate that infants of anaemic mothers are almost six times more likely to become anaemic by the first year of life, even after adjusting for several confounding factors, such as socioeconomic status and feeding practices (158). Anaemia during pregnancy is also correlated with other ABOs such as PTB, LBW, and maternal death (120, 158).

This high prevalence in Africa is generally because women may be pregnant or lactating for as much as half of their reproductive lives, although it may also be due to some parasitic infections (159). Additionally, haemoglobinopathies such as sickle-cell disease and infections such as malaria, tuberculosis and HIV also contribute to the high prevalence of anaemia in the SSA region. (139, 158).

Hence, in ANC, it is mandatory to perform a full blood count for all countries (139). The WHO guidelines recommend that haemoglobin should be measured at the first ANC visit and, if normal, measured again at 28–32 weeks and 36 weeks (139). High-dose haematinics should be prescribed to women with mild anaemia (Hb 8–9.9 mg/dl) and should be repeated in one month (139). If haemoglobin is < 10 mg/dL at more than 36 weeks, the women should be additionally referred to a hospital (139).

Hypertension/preeclampsia/eclampsia: It is estimated that 16% of maternal deaths in the SSA region are attributable to hypertensive disorders during pregnancy, with an incidence of preeclampsia/eclampsia ranging from 3 to 5% up to 10% (167). In fact, hypertensive disorders during pregnancy are the second leading cause, after haemorrhage, of maternal and perinatal deaths (12). Preeclampsia induces foetal and maternal complications, and it is more frequent, as previously mentioned, with advanced age, multiple pregnancies, nulliparity, and prepregnancy medical conditions such as chronic high blood pressure, type 2 diabetes, and renal failure (167). During childbirth, placental

insufficiency in preeclampsia and eclampsia leads to intrauterine foetal hypoxia or intestinal ischaemia (168).

According to the WHO, pregnancy-induced hypertension is defined after the 20th week gestation with two readings of diastolic blood pressure 90–110 mm Hg (4 hours apart) and with no proteinuria (169). Mild preeclampsia, by contrast, has a proteinuria up to 2+, and severe preeclampsia is defined by diastolic blood pressure 110 mm Hg or more and proteinuria 3+ or more. Eclampsia is characterized when convulsions occur (169). Therefore, diastolic blood pressure alone is an accurate indicator of hypertension in pregnancy (169). The presence of proteinuria changes the diagnosis from pregnancy-induced hypertension to preeclampsia (169). Regarding clinical manifestations, headaches, blurred vision, convulsions, and loss of consciousness are often associated with hypertension in pregnancy but are not necessarily specific to it, as in these settings, other conditions that may cause convulsions or coma include epilepsy, complicated malaria, head injury, meningitis or encephalitis and should be acknowledged (169).

Gestational diabetes mellitus: Blood glucose tests are used to screen for gestational diabetes mellitus, which is characterized by elevated glucose intolerance during pregnancy (139, 170). Hyperglycaemia first detected at any time during pregnancy should be classified as either gestational diabetes mellitus or diabetes mellitus in pregnancy, according to WHO criteria (170). Insulin resistance in the mother promotes the movement of nutrients towards the foetus, and typically, the infant of the diabetic mother is large for gestational age (170). Severe diabetes, however, can be accompanied by foetal growth retardation (170).

Maternal haemorrhage (antepartum): Antepartum haemorrhage refers to bleeding from or into the genital tract after the period of foetal viability and before delivery (171). Bleeding prior to 22 weeks of gestation is classified as miscarriage (169). Antepartum haemorrhage can occur in 3-5% of pregnancies worldwide and accounts for 30% of maternal mortality (171). Common obstetric causes are abruptio placentae, a ruptured uterus, or placentae praevia (169). Major obstetric haemorrhage will be addressed in section 2.4.2. Chapter 1.

Rhesus and ABO incompatibility: During pregnancy, it is important to have access to the pregnant women´s blood group and Rhesus (Rh) status (139). Rhesus-negative mothers can develop Rh antibodies if they have a Rh-positive newborn, causing haemolytic disease of the newborn in subsequent pregnancies (172). Haemolytic disease of the newborn (HDN) - also called erythroblastosis foetalis - can have two causes, Rh, which causes haemolytic disease more frequently, and ABO incompatibility (172). Rh incompatibility is approximately three times more likely in Caucasian babies than in African babies, and it is estimated that HDN affects three to eight newborns yearly for every 100 000 (172). Newborn disease can be associated with mild anaemia and hyperbilirubinemia due to the ongoing effect of rhesus antibody haemolysis on more severe manifestations such as kernicterus, which occurs in approximately 25% of cases (172). Kernicterus is caused by the build-up of bilirubin in the tissues of the central nervous system that can lead to developmental retardation, hypotonia, and hearing loss (172). This hyperbilirubinemia is mostly treated with phototherapy and, on rare occasions, exchange transfusion (172). Phototherapy is the first-line newborn treatment method with few side effects, and it is also efficacious in treating preterm infants (172). However, the best approach is still avoidance of maternal allosensitization (172). WHO recommendations for the Africa Region state that antenatal prophylaxis with anti-D immunoglobulin in nonsensitized Rh-negative pregnant women at 28 and 34 weeks of gestation to prevent RhD alloimmunization is recommended only in the context of rigorous research (139).

Blood group testing is also extremely important in ANC since blood transfusion can be needed as a life-saving emergency intervention (139). Most pregnancy-related complications, namely, severe anaemia, haemorrhage, sepsis, eclampsia, obstructed labour, and abortion complications, require timely availability of blood to save the life of the mother and the child, justifying why blood group is highly recommended during ANC screening (139, 171).

2.4. Intrapartum Factors

Major intrapartum complications and healthcare service-related factors have a key role in peri-neonatal deaths and adverse outcomes (54, 72, 173). Globally, the two most important factors responsible for the high rates of maternal and peri-neonatal deaths are the absence of quality maternal care and the nonexistence or deficiency of skilled routine emergency care, since the most common causes of these deaths are obstetric haemorrhage, hypertensive disease, and sepsis (72, 173-175). Moreover, maternal and newborn deaths and complications are also frequently the result of obstructed and prolonged labour, mainly in low-resource settings (174, 175).

The main healthcare service-related factors (delays, skilled maternal healthcare, emergency obstetric and neonatal care, assessment of progress of labour, use of the partograph, episiotomy, instrumental vaginal delivery, and caesarean section) and main obstetric complications (prolonged second stage of labour, obstructed labour, prolonged rupture of membranes, meconium-stained amniotic fluid, major obstetric haemorrhage and maternal near-miss) have specific roles in peri-neonatal deaths and in some adverse birth outcomes that should be understood for each specific setting and country (72, 173-175). Quality care during labour and birth is marked by a series of core competencies defined by the WHO, the International Council of Midwives, and the International Federation of Gynaecology and Obstetrics (FIGO) (176).

2.4.1. Healthcare service-related factors

Delays: In the SSA region, prevention of intrapartum complications is related to the "Three Delays Model": 1) delay in recognition of danger signs and decision to seek care more than 24 hours), 2) delay in reaching an appropriate source of care (more than one hour) and 3) delay in obtaining adequate and appropriate treatment in the health facility (more than one hour) (60, 177, 178). There is another factor that is related to pregnant women´s autonomy to maternity care and classified as autonomous if she decides alone or with her husband (jointly) to seek maternal and child healthcare; otherwise, she is not autonomous, meaning a husband alone or a third party deciding on the use of the services (60). As an example, ten preventable delays associated with peri-neonatal deaths in rural

areas of South Africa were identified as follows: 1) deaths related to inadequate equipment in neonatal units (4.9%); 2) nonexistent or poor ANC (3.5%); 3) inadequate intrapartum foetal monitoring (3.2%); 4) delay in seeking medical attention during labour (2.4%); 5) prolonged second stage of labour with no intervention (1.4%); 6) inappropriate response to rupture of membranes (1.2%); 7) lack of transport from home to the health facility (1.2%); 8) poor progress in labour and incorrect use of partograph (0.9%); 9) delay in medical personnel calling for expert assistance (0.8%); and 10) inadequate neonatal management plan (0.8%) (178).

Skilled maternal healthcare: Skilled maternal healthcare in low-resource settings encompasses a range of services, including ANC, skilled birth delivery care, and postnatal care. A skilled birth attendant is characterized as an accredited health professional (a midwife, doctor, or nurse) who has been educated and trained to manage normal uncomplicated pregnancies, childbirth, and the immediate postnatal period, and in the identification, management, and referral of complications in women and newborns (178). Worldwide, deliveries assisted by a skilled birth attendant increased from 62% in 2000 to 81% in 2018 (163). In SSA region, the proportion of births attended by skilled health personnel varies widely by country. According to the WHO, in 2017, the percentage of births attended by skilled health personnel ranged from 5% in South Sudan to 99% in Mauritius (177, 178). The regional average was 62%, which is lower than the global average of 81% (178). Focus on skilled maternal health care is essential because it significantly improves pregnancy outcomes (178-180).

Childbirth/Delivery: Spontaneous vaginal delivery at term is the normal outcome for pregnancy since childbirth is a natural event, and all deliveries should ideally be spontaneous and risk free (178). Currently, approximately 60% of pregnant women in SSA give birth at the primary level of care, namely in community health centres and district hospitals (181). However, even currently, many births occur at home with no formal contact with the healthcare system (182).

There is a huge contrast between high-quality standards from HICs and those from LLMICs (9). For instance, in HICs, with techniques such as continuous foetal heart monitoring, foetal Doppler, and scalp pH estimations, the degree of foetal compromise

can be evaluated early, and prompt and live-saving interventions can be put in place (9). However, in LLMICs, most peripheral centres are devoid of facilities for managing high-risk deliveries or providing essential newborn care (183). Frequent complications are prolonged labour and foetal distress, associated with maternal and foetal conditions such as preeclampsia, eclampsia, abnormal presentation, and cord accidents (184). Since complications occur and spontaneous vaginal deliveries are not always feasible, there is a need for recourse to instrumental vaginal delivery and caesarean sections to prevent maternal and peri-neonatal deaths and morbidity (184).

Instrumental vaginal delivery: Its use varies widely both between and within countries and may be performed as infrequently as 1.5% or as often as 26% (185). The application of an instrument to facilitate the birth of a child is a process that dates back to the late 16th century (185). Currently, the instrumental vaginal delivery (IVD) is an integral part of worldwide obstetric care (185, 186). The most frequently used instrument in resource-constrained countries is the vacuum or ventose (186). Vacuum deliveries are simpler to use because they are more tolerant of incorrect assessments of the foetal head position and are associated with lower rates of neonatal trauma, generally mild and self-limiting (186). This feature in theory makes it a safer instrument in relatively unskilled hands and it has therefore become the instrument of choice for many settings (186). Forceps are linked to higher rates of maternal trauma and require greater experience to use (186). The downsize is that IVD is a risk factor for foetal morbidity and mortality, as well as early and late maternal morbidity, including faecal incontinence (185).

Caesarean section: The optimal range for caesarean section rates, according to the WHO, is between 5% and 15% (139, 187). However, access to safe caesarean section in resource-limited settings is much lower, estimated to be 1% to 2% (187, 188).
Caesarean section is a life-saving intervention considered essential for antepartum haemorrhage, prolonged or obstructed labour, preeclampsia or eclampsia, and intrapartum foetal distress (188). It can avert major obstetric complications that lead to maternal, neonatal, and/or foetal death (188). The negative impact of caesarean section, in both the short and long run, is that it can compromise future pregnancies (109). Caesarean section can lead to complications, namely, postpartum infection, uterine

rupture, bladder injury, haemorrhage, thromboembolism, uterine scar, uterine rupture, placenta previa, placenta accreta, gravid hysterectomy after a secondary section and maternal death (109, 187-189). There is also growing evidence, albeit with different levels of strength, that it modifies the flora of the bowel of the newborn and interferes with the development of the child's immune system, therefore increasing the risk of allergies and obesity later in life (189). Furthermore, caesarean section delivered newborns had less skin-to-skin contact with their mothers during the immediate postpartum period, which is critical for the newborn, and this could be accompanied by difficulties for neonates to breastfeed within one hour of birth, putting the neonate at a higher risk of early complications (109, 189).

Episiotomy: Episiotomy rates in HICs are often below 30%; on the other hand, in LLMICs, these rates can be much higher, up to 70% (190). An episiotomy is an incision, extensively applied in obstetrics practice, made into the perineum for the purpose of enlarging the soft tissue outlet for a macrosomia or breech infant or to decrease the length of the second stage if the baby is in distress (191). However, according to WHO recommendations, episiotomy should not be performed routinely and has short- and long-term complications (169, 191). This intervention is only advised in cases of i) complicated vaginal delivery (breech, shoulder dystocia, forceps, vacuum extraction), ii) scarring from female genital cutting or poorly healed third- or fourth-degree tears and iii) foetal distress (169).

Assessment of progress of labour and the partograph: The partograph consists of key information about the foetal and maternal status and has a special role that leads to an on-time decision and intervention (174, 192). It allows improvements in foetal and newborn survival as well as significant reductions in unnecessary interventions (178). The WHO recommends the partograph to be used for monitoring all labouring mothers (174, 192). However, this toll is hardly used in the African maternity context (178). The main reasons are a lack of human resources, time pressure, stock-outs of partograph paper, deficient monitoring of maternal and foetal key indicators, particularly the foetal heart, as the traditional Pinard stethoscope may be inaccurately used, and Doppler ultrasound monitors

are not widely available, leading to delays in undertaking emergency care, particularly caesarean section (174, 178).

Emergency obstetric and neonatal care: Worldwide experience estimates that 15% of all pregnant women will develop obstetric complications, and that not all can be predicted through risk screening (178). A series of surveys in more than twenty African countries suggests that 15%, less than a third, receive Emergency Obstetric and Neonatal Care (EmONC) (178). The proportion of direct obstetric complications receiving timely treatment (met need for EmONC) should be increased by at least 50% to achieve maternal and newborn morbidity and mortality reduction (178). The EmONC was first developed by the WHO in 1992 and agreed on internationally by all United Nations organisations (181). This package is a list of lifesaving services or 'signal functions' that define a health facility about its capacity to treat obstetric and neonatal emergencies (181). EmONC can be classified as basic and comprehensive according to techniques available at the facility (178). There are seven **Basic** emergency care (**B**EmONC) signal functions and nine **Comprehensive** (**C**EmONC) signal functions (BEmONC and two others: perform safe blood transfusions and surgery with births by caesarean section) (178). BEmONC consist of providing the following skills: i) administration of parenteral (injection) antibiotics, ii) oxytoxics, iii) anticonvulsants, iv) manual removal of placentae, v) manual removal of retained products, vi) assisted (instrumental) vaginal births, and vii) basic neonatal resuscitation with bag and mask (178).
Universal access is particularly challenging in LLMICs due to specific requirements for infrastructures such as functioning operating theatres; human resources such as highly skilled clinical staff with fast response times, available 24 hours a day; and reliable supplies of blood, drugs, and equipment (193). However, of all the maternal, newborn, and child health packages, skilled childbirth care and EmONC are the strategies known to provide opportunities to save the most maternal and newborn lives (178, 193).

2.4.2. Main obstetric complications

Prolonged second stage of labour: The second stage of labour begins when the cervix becomes fully dilated and ends with expulsion of the neonate (194). Prolonged second stage of labour is usually defined as 2–3 hours for primiparous women and 1–2 hours for

multiparous women, with a longer interval for women with epidural analgesia during labour (194). Worldwide estimations report that second-stage labour exceeded 3 hours for 2.3% of primiparous women and 2 hours for 6.6% of multiparous women (195).
Prolonged second stage of labour increases the risks for instrumental vaginal delivery or caesarean section and can be due to foetus-pelvic disproportion (mechanical dystocia) and/or inadequate contractions (dynamic dystocia) and/or ineffective maternal pushing efforts in the second stage of labour (195).
Maternal adverse outcomes associated include intensive care unit admission, postpartum haemorrhage, episiotomy, 3rd or 4th degree perineal laceration, urinary retention, chorioamnionitis, and endometritis (194, 195). ABOs comprise foetal hypoxia and acidaemia leading to birth asphyxia, neonatal intensive care unit admissions, sepsis, seizures, and low Apgar scores (176, 195).

Obstructed Labour: The term obstructed labour indicates that the presenting part of the foetus cannot progress into the birth canal, despite strong uterine contractions (175). It is a preventable obstetric complication, estimated to affect 5% of all pregnancies and accounts for an estimated 8% of maternal deaths (175). It can occur due to cephalo-pelvic disproportion, a mismatch between the foetal head and the mother's pelvis, malpresentation and malposition (174).
Obstructed labour induces maternal dehydration, distress, and shock, which may result in intrauterine foetal hypoxia secondary to insufficient placental perfusion and the passage of meconium into the amniotic fluid (168). All the above can then increase the odds for birth asphyxia and other ABOs, as previously mentioned for prolonged second stage of labour (194, 195). In a SSA study, complications of obstructed labour were sepsis in 38.59%, stillbirth in 38.08%, postpartum haemorrhage in 33.54%, uterine rupture in 29.84%, and maternal death in 17.27% (175). The obstruction can be alleviated by means of an operative delivery, either caesarean section or other instrumental delivery, as previously described (186, 187).

Prolonged rupture of membranes: PROM is defined as rupture of membrane lasting more than 18 hours before labour (196). When it occurs before the 37th week of gestation it is called preterm premature rupture of membranes (196).

PROM is found in approximately 8%-15% of all pregnancies worldwide with a relatively higher incidence in Africa (196). Globally, up to 50% of premature deliveries and 80% of maternal clinical and subclinical infections have been associated with PROM with a fourfold increased risk of foetal mortality (196). PROM is also responsible for amniotic-fluid infections, spontaneous preterm birth and neonatal complications, such as, neonatal sepsis, respiratory distress syndrome, intraventricular haemorrhage, and necrotizing enterocolitis (197).

Meconium-stained amniotic fluid: A meconium-stained liquor of dark green or black colour, that is thick and tenacious, is classified as meconium-stained amniotic fluid, and it is significantly associated with ABOs and peri-neonatal mortality (198).
Globally, 10–20% and 15% of labouring mothers in the SSA region are estimated to have meconium-stained amniotic fluid (92). Meconium-stained amniotic fluid is a risk factor for increased peri-neonatal morbidity and mortality in both HICs and LLMICs (168). It is usually a predictor of ABOs such as i) meconium aspiration syndrome (5-10.5%), ii) lower Apgar score, iii) perinatal asphyxia, iv) increased rates of neonatal resuscitation, v) respiratory distress, vi) neonatal nursery admissions, vii) neonatal sepsis, viii) pulmonary disease and ix) death (12%) (168, 198). It is also associated with meconium-laden amniotic fluid embolism, intrapartum chorioamnionitis, puerperal endometritis, wound infection, increased risk of operative delivery and its complications (168).
Factors reported to increase the odds of meconium-stained amniotic fluid, are as follows: hypertensive disorders of pregnancy, prolonged labour, post-term pregnancy, oligohydramnios, IUGR, and LBW (168). Maternal factors, such as higher maternal age, tobacco, and cocaine use, are also associated with the passage of meconium into the amniotic fluid (168).

Major obstetric haemorrhage: Major obstetric haemorrhage is defined as haemorrhage occurring antepartum, intrapartum, or postpartum and leading to hysterectomy or blood transfusion ≥5 units of packed red blood cells or hypovolemic shock (199, 200). It is considered to be a marker of maternal near miss with critical outcomes, including shock, collapse or need for resuscitation, disseminated intravascular coagulation, renal failure, and low postnatal haemoglobin level (199, 200). Moreover, there are also associated

major morbidities in neonatal outcomes, including hypoxic ischaemic encephalopathy, cerebral palsy, neurodevelopmental disability or developmental delay, and neonatal anaemia, morbidities that affect the rest of the baby's life (199). These factors have a considerable impact on survival and clinical outcomes as well as the woman's experience of labour and birth and on health care service costs (199).

Intrapartum haemorrhage, major or severe, is defined as blood loss >1000 mL and complicates approximately 5% of all deliveries (199).

Postpartum haemorrhage is defined as blood loss ≥500 mL during vaginal delivery and ≥1000 mL during caesarean section (201). It is an obstetric emergency complicating 1%–10% of all deliveries and is deemed responsible for 30% to 50% of maternal deaths (202). There are several identifiable risk factors, although most cases occur unexpectedly (201, 202). The most common aetiologies for postpartum haemorrhage, referred to as the four Ts, are 1) tone: uterine atony (accounting for 70% of cases), 2) trauma: genital tract trauma, 3) tissue: retained products of conception and 4) thrombin: coagulopathy (202).

Notably, the above definitions may not be clinically relevant in SSA countries, where small amounts of blood loss may have detrimental outcomes in patients with preexisting severe (haemoglobin <7 g/dL) or moderate anaemia (haemoglobin 7-9.9 g/dL) (201).

Maternal near-miss and death: Due to the reality of maternal major obstetric risks, the WHO developed the maternal "near-miss" approach to assess and improve obstetric care by identifying women who nearly died but survived severe complications of pregnancy that occurred during pregnancy, childbirth or within 42 days after birth or termination of pregnancy (54, 60, 173). Measuring maternal "near-miss" in addition to maternal death facilitates the investigation and evaluation of health care interventions (173). Moreover, since the mother´s wellbeing is intimately related to the neonatal health outcome, a maternal near-miss event or death is a risk factor and is associated with ABOs as well as peri-neonatal mortality (60).

Maternal death is defined as the death of a woman while pregnant or within 42 days of termination of pregnancy from any cause related to or aggravated by pregnancy or its management (173). The maternal mortality ratio has also declined by 45%, although approximately 800 women still die each day from preventable causes related to pregnancy

and childbirth (173). Maternal mortality in SSA is among the highest in the world, approximately 500 to 1000 per 100 000 livebirths versus approximately 5-20 in high-income countries (173).

2.5. Neonatal and postpartum factors

Neonatal conditions and adverse birth outcome-associated factors were previously addressed in section 1.2 and 1.3.

Timely and appropriate management of life-threatening conditions immediately after childbirth and postnatally has a major impact on neonatal mortality and morbidity (4, 6, 43, 203). Thus, evidence-based interventions recommended for the postnatal period will be mentioned in this section.

2.5.1. Essential immediate newborn care: Includes simple, easy and cost-free interventions (204). As an example, regarding the timing of cord clamping, for healthy term births, the evidence now supports clamping between one and three minutes (203). This delayed cord clamping enables a longer time for the cardiorespiratory changes that occur at birth as the neonatal circulation is established; hence, it may also be of greater benefit for preterm babies with immature lungs and myocardium, although further evidence is needed for PTB (65).

Another important factor is the type of care of the umbilical cord since it is a frequent source of bacterial contamination and subsequent infection (94). There are a variety of recommendations on umbilical cord care between hospital and community settings and cultural beliefs, between countries, mainly HICs and LLMICs. The main focus has been the use of antiseptics, antibiotics, soap and water, dry cord care and hand washing (94). The use of chlorhexidine in community settings in LLMICs demonstrated a reduction in both infection and mortality by 27–56% and 23%, respectively (94).

Mother-infant skin-to-skin contact, meaning keeping newborns in skin-to-skin contact on their mother's chest and enabling them to breastfeed, is one of the evidence-based interventions for neonatal mortality reduction (203, 204). However, the reality in many SSA countries is the separation of mothers and newborns that are often placed under warmers or in cots (204).

Additionally, bathing delayed for 24 hours, vitamin K and vaccines given as per national guidelines, temperature monitorization, and complications should be identified and managed (178, 203).
In facility-based deliveries, newborns should receive an immediate check at birth and a full clinical assessment approximately one hour after birth and before discharge (203).

2.5.2. Emergency neonatal care package: The first neonatal emergency intervention needed is to provide neonatal resuscitation techniques, a set of interventions at the time of birth to support the establishment of newborn breathing and circulation (205). The concept of the "golden minute" highlights the importance of the first minute after birth, by which time a neonate should be breathing or receiving positive pressure ventilation with an appropriately sized bag and mask (205). The failure of the neonate to initiate and sustain respiration within the first minute after birth may result in the condition known as birth asphyxia, previously discussed in section 1.3.3.
Providing high-quality care for sick neonates with specialized support is not often possible in most LLMICs (205). In HIC settings, frontline nurses, midwives, physicians, and respiratory therapists are all trained and certified in neonatal resuscitation (9, 205). Moreover, most HIC units have more resources, with a neonatal resuscitation team that includes a neonatologist or pediatrician and a specialized Neonatal Intensive Care Unit (NICU) registered nurse (9, 205). A contrast with most LLMICs, where one nurse is providing care for both the birthing woman and newborn (178, 205). Associated factors for midwives who were less likely to have adequate skills in neonatal resuscitation were as follows: 1) younger age, 2) less experienced (<4 years of work experience), and 3) work in small, lower volume settings (fewer than four nurses and midwives per shift, less than six deliveries per day) as reported in a 2022 study conducted in Tanzania (205).
In addition to providing neonatal resuscitation techniques, healthcare facilities should also provide neonatal care for sick newborns (see Part III section 3.9). According to the WHO, all infants with a gestation <35 weeks or a birth weight < 2.0 kg should be admitted to a special care unit, as the smaller the infant is, the higher the risk (71, 178, 205). Management of neonatal common problems should follow the WHO guidelines available at the "Pocket book of hospital care for children: guidelines for the management of common illnesses with limited resources" (206).

2.5.3. Postnatal period: This period starts one hour after the third stage of labour and lasts up to 42 days after delivery (203, 207). It is considered to be the most neglected period for the provision of quality care (203). In low-resource countries, it is estimated that only 58% of women and 28% of newborns receive postnatal care within 42 days after delivery (207).

For home deliveries, the first postnatal contact should be within 24 hours of birth, followed by three additional visits on day 3, between days 7–14 and six weeks after birth (203). Additionally, the WHO and UNICEF issued a joint statement advocating home postnatal care visits for mothers who were unable to bring their newborn babies to a health facility, however, this is not available in most SSA countries (see Part III section 3.9.) (178, 203).

In the SSA region, common barriers, such as cultural, educational, social, and economic barriers, contribute to women not seeking postnatal services (178, 193, 207). On the other hand, ignorance of pregnancy-related complications, high parity, non-use of ANC, having birth outside health facilities, birthing with the help of untrained birth attendants, distance to health facilities and assumption that physical recovery is always smooth are also main contributors to low postnatal care attendance in these settings (207).

2.5.4. Mother´s knowledge of newborn danger signs: One important factor is the mother´s knowledge of key newborn danger signs (178, 205). The nine WHO-UNICEF lists of newborn danger signs include the inability to feed since birth or stop feeding, convulsions, fast breathing, severe chest in-drawing, high-grade fever, cold extremities, only moves when stimulated, or not even when stimulated, yellowish discolouration of extremities, and signs of local infection (umbilicus red or draining pus, skin boils, or eyes draining pus) (178, 205). A mother who scores above the mean is deemed knowledgeable; otherwise, it is deemed not knowledgeable (109).

Part II |Tracing the invisible

Tracing the invisible

Due partly to the emphasis on child mortality by *Health for All by 2000,* followed by the Millennium Development Goals, and now with the Sustainable Development Goals (SDGs), neonatal mortality levels are more precisely known than ever before (208, 209). Except for most resource-constrained countries were knowledge of mortality rates for stillbirths, early and late neonatal deaths and perinatal deaths is dependent on statistically modelled estimates (208). In fact, only 36 countries have high-quality nationally representative data on under5 mortality for 2021, while approximately half the world's countries have no data on neonatal mortality rates (209).
Beyond counting deaths, understanding the distribution of causes and associated factors of deaths is important for identifying appropriate interventions and programme priorities. Emphasizing the need for tracing and studying neonatal deaths and stillbirths since, currently, they are still mostly invisible (178).

1. Sources and lack of quality data

The gold standard for mortality monitoring is its measurement by complete vital statistics in a fully functional civil registration and vital statistics system (CRVS) (208). The definition of "complete" not only implies that all vital events are recorded, but also that timely and accurate information on the events is captured and analysed (208).

A country is defined as having a "complete registration" when it is able to achieve a 90% coverage of vital events. Moreover, achieving 100% coverage of birth registration and 80% of death registration is one indicator of progress toward SDG target 17.19 (208).

In SSA region, only Seychelles, Mauritius and Cape Verde have over 90% complete birth and death registration (208).

Therefore, there is a lack of complete vital registration systems in most SSA countries, and nearly all babies who are stillborn and half of all newborn deaths are not recorded in a birth or death certificate, and are never registered, reported, or investigated by the health system (8, 10, 29, 42, 43, 47). Moreover, it is worth noting that neonatal mortality rates can vary widely within a country, depending on factors such as geography, socioeconomic status, and access to healthcare services (178).

This means that for countries with lack of neonatal high-quality CRVS systems, neonatal mortality rates are estimated from census, modelling, raw data, verbal autopsy methods, sample surveys or household surveys (209, 210, 211).

Globally, the main sources are the United Nations Children's Fund (UNICEF), the WHO Maternal, Newborn, Child and Adolescent Health Data Portal, the United Nations Global SDG Database, the Mother and Newborn Information for Tracking Outcomes and Results (MONITOR), the UN Inter-agency Group for Child Mortality Estimation, the Demographic & Health Survey (DHS) from USAID, the Institute for Health Metrics and Evaluation (IHME), and the Countdown to 2030 (211).

Household surveys, such as the UNICEF-supported Multiple Indicator Cluster Surveys (MICS) and the US Agency for International Development–supported Demographic and Health Surveys (DHS), which ask women about the survival of their children, are the basis of child and newborn mortality estimates for most LLMICs (211, 212, 213).

Originally, MICS started in the mid-1990s for 60 countries, and rounds occurred every five years (212). Currently, periodicity is every three years (212). However, countries such as Mozambique and Equatorial Guinea have only had one MICS since 2000, with no other survey in the past twenty years (212, 213).

All the above explains why different neonatal mortality rates are reported for the same country and for the same period, since sources use different methodologies, as can be observed comparing the rates for NMR for PALOP countries in Table 1 and Chart 1.

Furthermore, estimates may underestimate the actual prevalence of neonatal adverse birth outcomes since many babies are not weighed at birth and births may occur at home or in small maternity units without official reporting in these settings (1, 4, 178). Additionally,

there are also several potential sources of bias in the proportion of different causes of neonatal deaths. For instance, early neonatal deaths may be misregistered as stillbirths (214). Moreover, the measurement tools used in resource-constrained settings, when existing, particularly verbal autopsy, underestimate intrapartum-related neonatal deaths, misclassifying them as stillbirths (214). Furthermore, comorbidity may be complex, since neonatal infection and acute intrapartum events are synergistic, and the direct cause of death may be debatable (214).

Other differences are also seen between HICs and LLMICs. In HICs, the definition of intrapartum-related neonatal deaths is restricted to deaths subsequent to neonatal encephalopathy with multiorgan dysfunction, documented acidosis, and proven intrapartum insults (214). However, the use of this definition is not feasible in LLMICs and misses an important group, namely, those infants who die immediately after birth if resuscitation is unavailable or fails (214). Moreover, in countries with high NMRs, there is a greater proportion of deaths caused by infections and tetanus, limited access to obstetric care and acute intrapartum events that more frequently result in stillbirth than neonatal death (3, 4, 214). All these translate in huge complexity in understanding what is truly happening in most resource-constrained countries in terms of neonatal death and adverse outcomes.

Hence, data must be interpreted with caution (59). This limited availability of high-quality data over time for many countries makes generating accurate estimates of neonatal mortality a considerable challenge (209). Moreover, these substantial data gaps place enormous challenges to policy- and decision-making for these settings. Emphasizing the need for tracing invisible neonates and gaining real data for resource-constrained countries.

2. Targets for 2030

Even though most newborns and stillbirths are still invisible, it is recognized that the high mortality rate estimates for LLMICs must be reduced and prevented.

In fact, it was only recently, in 2015, that newborns started to receive special attention since SDG 3.2 set the first ever global target for newborn survival by 2030 (8). SDG 3.2 aims to eliminate preventable child mortality, with the decline in neonatal death to less than 12 per 1000 livebirths (SDG 3.2.2.), and reduction of death of children younger than five years to fewer than 25 per 1000 livebirths (SDG 3.2.1.) for each country by 2030 (8). Stillbirths were recently included and a target of 12 stillbirths per 1000 livebirths or less by 2030 was set (46).

Estimations indicate that of a total of 204 countries, only 139 (68%) are on the road or have already achieved the SDG 3.2 target of fewer than 12 neonatal deaths per 1000 livebirths (8). However, at current rates of progress and due to the COVID-19 pandemic burden, this target may not be met, as there are 65 countries behind the level of progress needed, with approximately 40 countries needing to double their current progress (8, 37).

The SDG agenda is supported by various global initiatives and strategies, such as the Global Strategy for Every Newborn Action Plan (ENAP) (215), Women's, Children's, and Adolescents' Health (Global Strategy) (216), Ending Preventable Maternal Mortality (217), and the Global Financing Facility in Support of Every Woman Every Child (218). The innovative and promising Implementation Toolkit for Small and Sick Newborn Care, co-chaired by the UNICEF and Nest360, is an example of a recent initiative expected to be a game-changer in these countries (219). These initiatives have set out goals and targets for ending preventable maternal and newborn deaths, as well as stillbirths, by 2030 (177, 220).

Moreover, fighting adverse birth outcomes is also a global priority established by the ENAP through identifying and implementing low-cost interventions to reduce them as a crucial public health importance (215). ABOs remain leading contributors to the global burden of disease and neonatal mortality in HICs and LLMICs, despite the huge gap between those two completely different realities. As previously mentioned, if survival

occurs, the small and sick newborns are at the greatest risk of disability (6, 80). Most have long-term consequences on neurological and cognitive development, cardiovascular disease, pulmonary disease, obesity, and severe disabilities such as blindness or low vision, as well as hearing loss, with a significant psychological impact, emotional, and financial strain on the family, society, and a huge burden for the child, mostly on those living in a low-resource setting (34, 92, 164, 80).

More recently, studies have examined the potential long-term human capital gains of reducing these adverse birth outcomes in LLMICs (80, 222, 223). One of the studies identified a substantial potential gain in schooling and lifetime income to gain from reducing ABOs to theoretical minimum values across 121 LLMICs (80). Then, it is expected that new interventions targeting the peri-neonatal periods are bound to reduce ABOs and provide these babies with a better future (178, 223).

Nonetheless, the future seems to be promising, since initiatives undertaken in previous decades have led to substantial reductions in ABOs and childhood mortality, mainly in HICs (215). Evidence shows that over two-thirds of newborn deaths could be prevented through the high coverage of cost-effective, low-tech maternal and newborn health interventions (110, 215).

3. High-impact solutions

From data to decisions: If the reality is unknown, is it worthwhile doing anything?

There is evidence that the universal implementation of some essential interventions could avert up to 72% of neonatal deaths in 75 countries (223). Considering the high rate of lives that can be saved with feasible, cost-effective care, resource-constrained countries should be able to implement the most high-impact solution (127, 215, 223-226). The main interventions and impact on the reduction of each cause of neonatal death are described in Table 2.

Table 2 | Cause-specific effect of intervention packages for reduction of main causes of neonatal mortality delivered at different periods

Nature of intervention (main elements of intervention packages)		Reduction: all-cause neonatal mortality	Cause-specific mortality reduction				
			Serious infections	**Tetanus**	**Birth asphyxia**	**PTB**	**Congenital anomalies**
Preconception	Folic acid supplementation	40-85%*					1-10%
	Family care[a]: clean delivery, hygienic cord care, thermal care, breastfeeding	10-50%	20-50%	75-85%			
Antepartum	ANC	10-20%	<1-5%	80-95%	10-20%	<1-5%	-
	Malaria (IPTp-SP)	10-30%	10-20%	50-70%	30-45%	5-10%	-
	Detection and treatment of asymptomatic bacteriuria	20-55%**	-	-	-	5-14%	-
Intrapartum	Skilled birth care	20-30%	10-20%	50-70%	30-45%	5-10%	-
	Neonatal resuscitation	5-20%	10-20%	50-70%	30-45%	5-10%	-
	Emergency obstetric care[b]	10-15%	-	-	20-60%	-	-
	Intrapartum antibiotics	15-45%***	3-9%	-	-	-	-
	Antenatal corticosteroids	25-50%	-	-	-	25-50%	-
Postpartum	Extra care for LBW[b]:	20-40%	1-10%	-	-	20-50%	-
	Case management for pneumonia	10-35%	20-55%	-	-	-	-
	Emergency neonatal care:	15-50%	30-70%	-	0-5%	15-40%	-

[a]A clean environment has a 25-60% reduction in the cause-specific neonatal mortality rate due to diarrhoea
[b]management of complications—obstructed labour, haemorrhage, hypertension, infection
[c]extra warmth, hygiene, feeding
*incidence of neural tube defects, **incidence of prematurity or low birthweight, ***incidence of infections

Source: Table adapted from reference_ Evidence-based, cost-effective interventions: how many newborn babies can we save? Lancet, 2005 (223). Available at: http://dx.doi.org/10.1016/S0140-6736(05)71088-6

The main interventions known to have a high impact on adverse birth outcome reduction and/or prevention will be briefly considered next, following the order addressed in Part I.

3.1. Stillbirths: Most stillbirths are preventable with quality health care during pregnancy and childbirth, especially in LLMICs (44). For example, simple techniques, such as foetal heart rate monitoring and labour surveillance and prompt interventions when needed, are crucial and estimated for preventing 832 000 intrapartum stillbirths and reducing early neonatal deaths (178, 192). These strategies will be further considered for intrapartum interventions.

3.2. Early neonatal deaths: Different strategies are available according to whether it is a HIC or LLMIC setting (55). In LLMICs, most conditions leading to ENND are preventable with relatively easy and cost-effective interventions such as delivery at a hospital, training health care workers in resuscitation practices, simplified algorithms that allow for early detection of perinatal infections, and early initiation of breastfeeding and skin-to-skin care (55).

3.3. Preterm babies: Preventing PTB is now one of the most urgent goals to make further progress in delivering the SDG target of reducing the mortality of children younger than five years (69, 226).

The 2015 WHO guidelines set key interventions to improve premature birth outcomes that can be provided to the mother: antenatal corticosteroid injections before birth, antibiotic prophylaxis when her water breaks before the onset of labour, and magnesium sulphate to prevent future neurological impairment of the child. To the premature baby are thermal care, feeding support, Kangaroo Mother Care (KMC), plastic wraps, continuous positive airway pressure therapy, surfactant, and oxygen therapy for the newborn (65, 70, 226).

In 2022 the WHO provided 11 new recommendations for PTB and LBW care and one new good practice statement (227). Strong, high-certainty evidence was granted for KMC by continuous and prolonged skin-to-skin contact starting as soon as possible after birth with support for exclusive breastfeeding or breastmilk feeding (227). Other measures are to provide probiotics for gut microbiome health during infancy, emollient therapy to

support skin barrier function, and methylxanthines (particularly caffeine) for prevention and treatment of apnoea (227).

Another very important strategy is to minimise long-term morbidity, namely, pulmonary disorders (70, 224). Much progress in neonatal care is relatively recent with exogenous surfactant only given to those born in the early 1990s, a technique not available in most SSA countries (69, 224). Not all preterm births will be preventable, and neonatal intensive care standards are crucial to improve survival and minimise long-term sequelae, although they are still a mirage in most low-resource constrained countries (71, 218, 224). The reality is that many of these standards are currently far out of reach for SSA countries, where the mortality of those born before 37 weeks gestation remains extremely high (69, 228). Scaling up neonatal care is essential and will be further considered for neonatal/postpartum interventions (214, 218).

3.4. Low birth weight: LBW is a preventable public health problem with long-term consequences, such as the onset of noncommunicable disease in the life course (75, 79). SDG 3 emphasises reducing neonatal deaths caused by LBW babies' complications by the implementation and utilisation of KMC in resource-constrained countries, as previously mentioned for PTB, which has been proven to reduce LBW mortality by almost 50% (228).

3.5. Intrapartum birth asphyxia: For resource-constrained settings, there is the need for scaling up birth deliveries at health facilities, as well as reinforcement of the health structures and training of the professionals on neonatal resuscitation techniques (88). Evidence from previous studies demonstrates that facility-based basic neonatal resuscitation can prevent up to 30% of intrapartum-related neonatal deaths (204).

The implementation of the Essential Newborn Care Course in resource-constrained countries enhances the training and improves neonatal outcomes, providing the basis for the essential care of every newborn: immediate care at birth, resuscitation when needed, breast milk feeding, thermal care, prevention of infection, recognition, and response to danger signs (229). For neonatal encephalopathy, early cooling therapy for babies with neonatal encephalopathy is potentially applicable more widely, even in LMICs, and

requires early and specific identification of babies with acute intrapartum brain injury (213, 230).

3.6. Neonatal Sepsis: In HICs, the prevention of sepsis relies on a strong healthcare system, an excessively high degree of sanitation, and other measures, such as the promotion of a healthy lifestyle and microbiome (94). On the other hand, neonatal sepsis in SSA countries is still hindered by a lack of rapid, accurate tests and poor access to medical care (90). Providing an increasing number of hospital births in a clean environment, proper umbilical cord care and the opportunity to offer parental education on danger signs are key strategies in tackling neonatal sepsis in these settings (94). Novel neonatal sepsis diagnostic tools—from biomarkers to molecular diagnostics - will offer potential for more rapid and sensitive detection of neonatal sepsis, mainly in SSA settings (90).

3.7. Congenital malformations: Early detection of congenital malformations, can facilitate life-saving treatments and prevent progression towards some physical, intellectual, visual, or auditory disabilities (97). As an example, structural congenital anomalies can be corrected with paediatric surgery and early treatment can be administered to children with functional problems such as sickle cell disorders, and congenital hypothyroidism (97). LLMICs should promote primary prevention and improve the health of children with congenital anomalies by i) developing and strengthening registration and surveillance systems, ii) developing expertise and building capacity, iii) strengthening research and studies on aetiology, diagnosis and prevention and iv) promoting international cooperation (97).

3.8. Intrapartum complications: There are known interventions and guidelines aimed at reducing major intrapartum complications in resource-constrained settings, and FIGO has made several recommendations in the past 20 years (176).

Some main strategies are as follows:

i) Prompt recognition and early referrals of pregnant women with complications from district facilities to high-level maternity units (176, 178, 231). Providers in district maternities should be trained to be experts in the early detection of complications through

foetal-maternal follow ups aided by different diagnostics (ultrasound, cardiotocography), which should always be accompanied by immediate decisions for emergency obstetrics and newborn care interventions (231). The use of portable point-of-care ultrasound technology during the third trimester is a successful tool in several LMICs across the world by trained community-based health midwives (231). This enables them to detect three risk factors for intrapartum-related neonatal/foetal death: 1) noncephalic presentation (the foetus presenting with a body part other than its head first, e.g., breech), 2) multiple gestation (e.g., twins), and 3) placenta previa (when the placenta is positioned low on the uterus, thus partially or fully covering the cervix, often leading to haemorrhage) (231).

ii) Implementation of the "Safe Childbirth Checklist" tool from the WHO (232). It is a tool aimed at assisting the daily practice of midwives and nurses in maternities (232). It contains items addressing the major causes of maternal death, intrapartum-related stillbirths, and neonatal deaths, especially in LLMICs, namely, haemorrhage, infection, obstructed labour, hypertensive disorders, inadequate intrapartum care, birth asphyxia, and complications related to prematurity (232).

iii) Give key strategies to empower pregnant women to avoid some intrapartum complications through a Birth Preparedness and Complication Readiness Plan (60). Pregnant woman should be able to implement at least five of the eight WHO recommendations: ascertained birthplace and birth attendants, established emergency transportation; put the money asides, identified labour, and birth companion; identified nearest health institution; identified blood donors if necessary, and identified care provider for children at home while the mother is away (60). Having this plan will enhance the use of skilled maternity care and reduce serious obstetric conditions through the well-timed use of facility care (60).

iv) Promoting the use of intermittent auscultation of the foetal heart rate with either a Doppler ultrasound device or a Pinard foetal stethoscope (233). Assessment of foetal wellbeing by computerized cardiotocography (CTG) throughout labour and delivery is vital for identifying and averting intrapartum foetal compromise and is estimated to reduce the rate of babies' deaths around the time of birth by 80% when compared with traditional cardiotocography (233). Thus, this cost-effective technology will easily improve the intrapartum quality of care (176).

v) Partograph is a cost-effective and affordable tool designed to provide a continuous visual view of labour progress for the prevention of prolonged and obstructed labour (173). Additionally, it consists of key information about the foetal and maternal status and has a special role that leads to an on-time decision and intervention (173). Strategies to better use the partograph should be implemented in LMICs according to WHO orientations, namely, to start plotting when cervix ≥4 cm, then cervix should dilate ≥1 cm/hr. Partograph monitoring should consist of 1) every 30 min: plot heart rate, contractions, and foetal heart rate; 2) every two hours: plot temperature and 3) every four hours: plot blood pressure (231-233).

vi) Providing timely interventions can reduce 60% to 70% of cases of eclampsia if diagnosed when first signs and symptoms appear; the use of a partograph to monitor labour can identify slow progress in labour, and adverse outcomes can be prevented through interventions such as oxytocin infusions; if signs of obstructed labour appear, assisted childbirth is needed and many breech births can be prevented by external cephalic version (178).

vii) Major obstetric haemorrhage complication reduction was achieved with the Women Trial, demonstrating that death from postpartum haemorrhage, mainly in the SSA region, can be reduced by approximately 30% if tranexamic acid is administered at the onset of bleeding, a relatively inexpensive intervention (202).

viii) For instrumental vaginal delivery reduction, some strategies are recommended, namely, companionship in labour, active management of the second stage with the active ingredient synthetic oxytocin and an upright birth posture (185).

3.9. Neonatal and postpartum care: More than half of all neonatal deaths could be averted with care being provided during the postpartum period: 1) 30% of all neonatal deaths can be averted with care of small and ill neonates, 2) 12% with care of healthy neonates, and 3) 10% with immediate newborn care (178).

The high-impact solutions for resource-constrained countries are as follows:

i) Early essential newborn care: in resource constrained settings, newborn deaths can be prevented through a set of simple, cost-effective interventions that benefit all mothers and newborns. At its core is First Embrace, a life-saving practice that promotes 1) drying the baby immediately and thoroughly after birth; 2) immediate skin-to-skin contact between

mother and baby for no less than 90 minutes; 3) clamping the cord after pulsations stop, cutting the cord with a sterile instrument; and 4) initiating exclusive breastfeeding when cues occur (such as drooling, tonguing, rooting, biting hand) (229).

ii) Prophylactic antibiotics: should be given to neonates with documented risk factors for infection, such as membranes ruptured >18 h before delivery or if the mother had a fever >38 °C before delivery or during labour and/or foul-smelling or purulent amniotic fluid (206). Such approaches would be a safe and cost-effective strategy, especially in resource-constrained countries (93).

iii) Neonatal complications: The main goal is to provide Level 2 neonatal care (214). The ENAP calls for 80% of districts of every country to have at least one hospital that provides Level 2 inpatient newborn care by 2025, including respiratory support with continuous positive airway pressure (CPAP) (214). Thus, facility-based clinical care of ill newborn babies, is crucial even for low-resource settings, although they are still currently non-existent in many SSA countries or are extremely resource-constrained (218).

3.10. Continuum of care: Promotion of the continuum of care, from antenatal to postnatal care, is an excellent opportunity to enrich mothers´ knowledge and enable them to have an active role in neonatal mortality reduction (100, 125, 178). It is estimated that up to 67% of neonatal deaths could be prevented by improving the coverage of common maternal, newborn, and child health care to 90% of reproductive age women (100). Thus, promoting maternal early screening and treatment of noncommunicable diseases by health care providers should also be promoted even in resource-constrained settings as a key to promoting infant health and reducing ABOs (91), namely:

i) Avoidance of birth intervals of less than 2 years is estimated to prevent 2 million of the 11 million deaths per year of children under5 years old and could also improve the opportunities for economic development of women and their families (133).

ii) Early identification and management of maternal chronic diseases including mental health, prior to conception. For instance, delaying pregnancy until the control of the underlying chronic diseases is one of the objectives of preconception family planning services (91, 126, 127). Moreover, anaemia and obesity, vaccine-preventable diseases such as tetanus and rubella, and personal habits such as tobacco and alcohol use, all

contribute to poor reproductive outcomes and could be modifiable with adequate preconception healthcare (135).

iii) Advanced maternal age is one of the nonmodifiable risk factors for pregnancy, and the promotion of early enrolment of women in preconception care may help couples to make a wise reproductive plan (41, 102).

iv) Creating awareness about family planning different method types and ensuring that women's fertility needs are met effectively is mandatory, especially in LLMICs (41).

3.11. Adolescent pregnancy prevention: The inclusion of adolescents in the SDG marked a further step towards a system for tracking adolescent health and adolescent pregnancy (234). There is a vast package of interventions aimed at reducing early pregnancies and motherhood in resource-constrained settings (114). One useful strategy to reduce adolescent pregnancies is that girls at risk of isolation and depression must be signalized and addressed early (114, 235). Timely intervention can help reduce unwanted teen sexual activity and pregnancy (114, 235). The school environment should be used to identify these girls (114, 235). Additionally, when pregnancy has occurred, the readiness of support structures that can share childcare responsibilities within the home, plays an essential role in ensuring that adolescent mothers return to school (235).

The goal is to know which of the high-impact interventions should be implemented with priority in a specific country. This is only effectively achieved by filling the evidence gap by studying the country context in terms of burden and associated factors of perinatal and neonatal mortality and morbidity

PART III | Sao Tome & Principe

The health status of the population, including neonatal health, is determined by several factors, as previously discussed. Characteristics such as the geographic context, economy, epidemiological environment, housing conditions, lifestyles, beliefs, attitudes, and behaviours can have an impact on neonatal outcomes (114). With this in mind, we will first consider the above factors for the Democratic Republic of Sao Tome & Principe, hereafter called Sao Tome & Principe (STP), the country chosen for this PhD research. Second, healthcare service-related factors, maternal characteristics and antepartum, intrapartum, and postpartum features currently known for STP will be addressed.

1. Country´s profile

1.1. Geographic context

It is an archipelago in the Gulf of Guinea (Figure 8), and it is the second smallest country in Africa, after the Seychelles (236). It distances 380 km off the coast of Africa, is crossed by the equator and has two main islands, Sao Tome (859 km^2) and Principe (142 km^2) (236). The isolation of STP has also generated unique biological diversity and particular epidemiological characteristics; it has no land borders but is located relatively close to the coasts of Gabon, Equatorial Guinea, Cameroon, and Nigeria (236). It features a tropical wet and dry climate with a relatively lengthy wet season (October to May) and a short dry season (June-September) (236).

1.2. Political system

Parliamentary democracy with a semipresidential system in which executive power is exercised by the prime minister, who is the head of government and shares with the President of the Republic certain spheres of power, such as international relations, diplomacy, and national defence (237, 238). The country belongs to the Small Island Developing States. It is highly limited by its insularity, fragility, and limited resources (236).

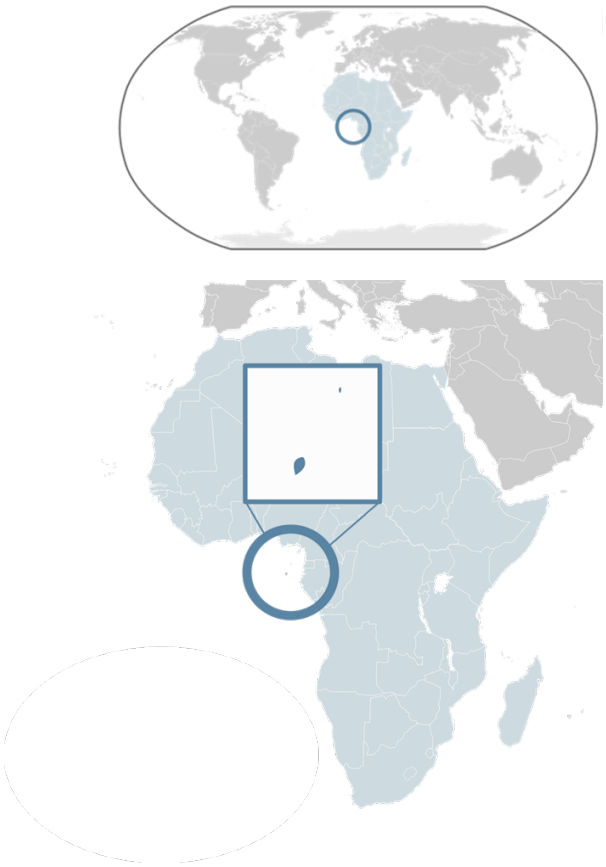


Figure 8 | Map of Sao Tome & Principe islands in the Guinea Gulf

Adapted from:

https://en.wikipedia.org/wiki/S%C3%A3o_Tom%C3%A9_and_Pr%C3%ADncipe#/media/File:Location_S%C3%A3o_Tom%C3%A9_and_Pr%C3%ADncipe_AU_Africa.svg

The capital city is Sao Tome in the Água Grande district. The country is divided administratively into seven districts (Água Grande, Cantagalo, Caué, Lembá, Lobata and Mé-Zóchi) and an Autonomous Region (Principe Island or Pagué) as represented in Figure 9 (236).

Portuguese is the official language spoken by approximately 98.4% of the country's population and is one of the six PALOP countries (236- 238). Restructured variants of Portuguese or Portuguese Creoles are also spoken, such as Forro, Cabo Verde Creole (8.5%), Angolar (6.6%) and Lunguié (1%) (238).

1.3. Sociodemographic and economic characteristics

It has a population of 227.000 (2022), with an annual birth cohort of 6.000-7.000 (approximately 19 births per day), while the total fertility rate is 3.8 births per woman (239). Among young women, 27% gave birth by age 18, and the country has an adolescent birth rate estimated to be 86 (number of births per 1000 women ages 15-19) (240). The life expectancy is 70 years old (239, 240).

It is a young country, with 41.8% of the population being less than 14 years old and more than 60% of the population being under 25 years of age (239). Approximately 68% of the STP population is urban, and it is projected to reach 70% in 2030, living in the capital, the city of Sao Tome (241, 242). Approximately 35.1% of children live in the capital, providing an overall view of the mothers' residency in the country (242). Trindade is the second most populated subdistrict, with 10.9% of all children (242). The subdistricts of Neves, Santana and Bombom are inhabited by 7%, 6.3% and 5.4% of children, respectively. Each of the 13 subdistricts remaining are populated by less than 5% of the children (242).

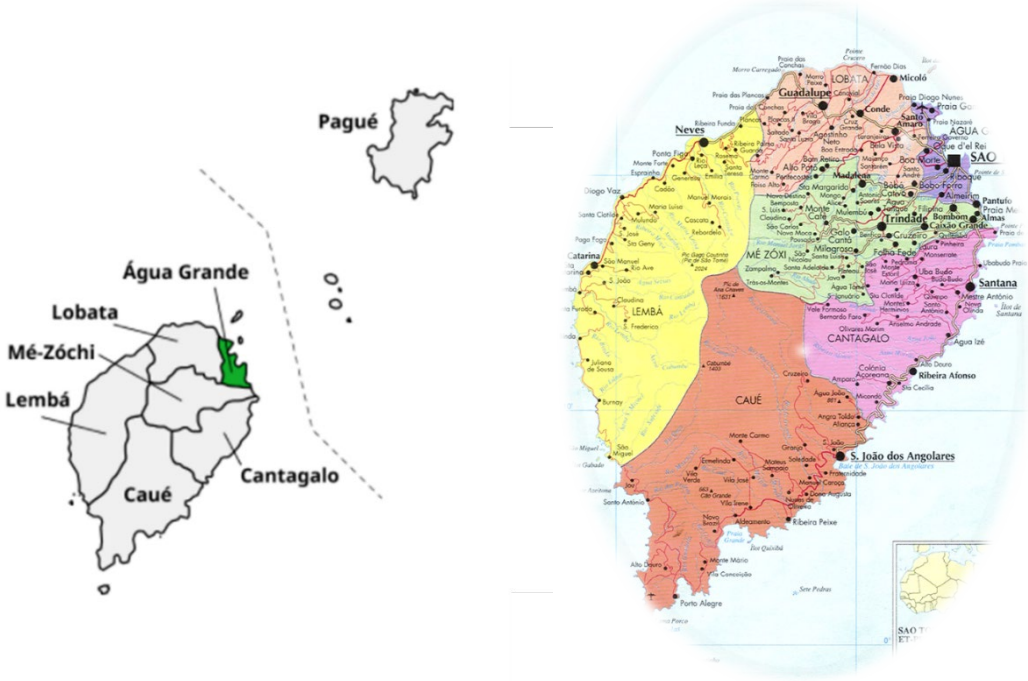


Figure 9 | Districts of Sao Tome & Principe

Adapted from reference (242).

Sao Tome and Principe is classified as a Lower Middle-Income Country (241). The World Bank estimates that approximately one-third of the population lives on less than the lowest international poverty line of $1.90 per day, and over two-thirds is poor, using $3.20 per day (241). The Human Development Index (HDI) value for the country is 0.625 (rank 135), a medium human development category—positioning it at 135 out of 189 countries and territories (241). From PALOP countries, Sao Tome & Principe is compared with Cape Verde and Equatorial Guinea, which have HDIs ranked 126 and 145, respectively (241).

1.4. Epidemiological profile

The epidemiological profile is marked by communicable diseases that continue to be a public health problem (242-244). These islands have all environmental, economic, and social conditions that favour the occurrence of infectious conditions, mainly in children (242). The country has been vulnerable to epidemics, with outbreaks of rubella in 2015, diarrhoea caused by rotavirus, necrotizing cellulitis in 2016/2017, and recently, during 2021, the first cases of dengue were reported in STP (242). Regarding COVID-19, STP had the first wave in 2020, and in 2021, it suffered a second and third wave of COVID-19, accounting for 2.836 new infections and a total of 41 deaths (36).

Malaria: Over the past decade, the country has made remarkable progress in the fight to control malaria and stop it from spreading and achieved an epidemiological situation of hypo-endemicity (242). The national average positivity rate is 2.7% (242). The goal is to reduce the incidence of malaria to less than 1 (one) case per 1000 inhabitants in all districts of the island of Sao Tome and to 0 (zero) indigenous cases in Principe Island (242). STP implemented the WHO package of interventions for preventing and controlling malaria during pregnancy, including promotion and use of insecticide-treated nets, appropriate case management with prompt, effective treatment, and administration of IPTp-SP in areas with moderate to high transmission of *Plasmodium falciparum* (242).

Tuberculosis: Tuberculosis is a national public health problem affecting mainly adults, young people and people living with HIV/AIDS (242). The national Tuberculosis program reported 91 TB cases for 2020 (242). A reduction compared to the 152 cases in

2018 (242). The detection rate is 79%, and the therapeutic success of detected cases is 71% (242).

Hepatitis B virus infection: The country is highly endemic for chronic hepatitis B virus infection, with a seroprevalence of hepatitis B surface antigen (HBsAg) of 10% in men and 6.1% in women (245). The first approach to this problem was made in 2002 with the introduction of selective hepatitis B birth-dose vaccination (Hep-BD), targeting infants born to chronically HBV-infected women identified by HBsAg screening during routine prenatal visits (245). Hepatitis B birth-dose vaccination coverage among infants born to HBsAg-seropositive women is estimated to be 92%, and both one-dose (98%) and three-dose coverage (96%) of the pentavalent vaccine (which includes diphtheria, tetanus, pertussis, hepatitis B, and Haemophilus influenzae b) are high, meaning that most infants will receive the complete series of HepB vaccinations (245). The second approach was undertaken recently, in 2018, with expansion to universal newborn HepB-BD without maternal screening (245, 246).

HIV: Due to insularity and preventive measures implemented in the past decades, it has a low HIV prevalence epidemic that has been reducing from 1.5% in 2008 to 0.5% in 2014 (246). Mortality showed an increasing trend between 2011 and 2014 (from 25 cases to 41); however, it has been decreasing, with 36 cases in 2016 (246).
In pregnant women, the HIV prevalence rate has been decreasing over the years, from 1.5% in 2008 to 0.3% in 2017 (246). The rate of HIV transmission in children born to infected mothers was 3.18% in 2016 and zero in 2021 (246). This success of zero vertical transmission is a key improvement compared to similar SSA countries where HIV MTCT is a high cause of child morbidity and mortality (242, 246).

Syphilis: Syphilis in pregnant women significantly decreased from approximately 1.8% in 2008 to 0.8% in 2017 (247). There were no cases of congenital syphilis during that period between 2008 and 2017 (246, 247).

Neglected Tropical Diseases: Lymphatic filariasis, schistosomiasis, soil-transmitted helminths (STHs) and leprosy are the four endemic Neglected Tropical Diseases (NTDs) in Sao Tome & Principe (242, 243).

The prevalence of intestinal parasitic infections (IPIs) has only been studied in children (243, 248-253). The STHs most prevalent in the country are ascariasis, trococephaly and hookworm, whose average prevalence is 33.1%, 58% and 4.6%, respectively (247). STH control strategies are focused on mass drug administration but only specifically targeting primary school-aged children (252). The control of STH infections in pregnancy consists of routine antenatal care through stool collected twice during pregnancy (139). Infected pregnant women receive treatment in the second or third trimester on a case-by-case basis (243, 247).

Schistosoma intercalatum (*Schistosoma guineensis* seems to reflect the current molecular terminology although *Schistosoma intercalatum* will be used in this research) is the only Schistosoma species endemic, particularly on Sao Tome Island, with an average prevalence of 7.6% (243, 253).

Regarding lymphatic filariasis, the 2015 study revealed a zero prevalence of *Loa loa* and onchocerciasis in the country, while the prevalence of lymphatic filariasis, endemic in all districts, ranges from 0.5% (Água Grande and Mé-Zóchi) to 3.9% (Lembá) (243).

In terms of health surveillance, Sao Tome and Principe have a national public health laboratory, which can provide diagnostic and surveillance services for infectious diseases (254). However, there are still gaps in the coverage and quality of disease surveillance, as well as challenges with data sharing and analysis (254).

1.5. National Health System

The health system is organized into four health regions, the North Region (districts of Lobata and Lembá), the Central Region (districts of Água Grande and Mé-Zochi), the South Region (districts of Caué and Cantagalo) and the Autonomous Region of Principe or Pagué (Figure 9) (254).

The country has 38 health units, including six health centres, 30 health posts, two reproductive health centres, one central hospital, which is the only reference hospital - Dr. Ayres de Menezes (HAM), plus one regional basic hospital on Principe Island, the Hospital Manuel Quaresma Dias da Graça (254). There are 22 community health posts (254). The health centre has a general practitioner responsible for outpatient care and a

small inpatient unit (254). Community health posts receive support and supervision from the health centre (254). Its activities are carried out under the direct responsibility of a general nurse and the district team that periodically travels from the district level into the communities (254). Community Health Posts belong to rural communities and receive support to provide basic care and first aid and ensure health promotion (254). This health coverage in terms of infrastructure is not equitable, as it varies between three health centres/posts for every 15577 inhabitants in the country's capital and one health centre for every 1139 inhabitants in Principe (254). Users are not registered in a particular health centre, and citizens can go to any health centre in the country for any health care (254).

There is no health insurance in STP and very little private health infrastructure (254).

The national health system and the STP Ministry of Health (MoH) have serious constraints due to limited human resources capacity, deficits in health facilities, lack of funding and absence of partnerships (238). Aggravated by a context of widespread poverty, lack of structural basic sanitation, frequent electricity blackouts and shortage of clean water (238). Moreover, shortcomings of political governance, which determine the frequent change of governments and ministers, end up aggravating this situation (254). The country is highly aid dependent, but given its size and insularity, it has a limited donor presence (236, 237). Approximately only 40% of funding for health programs and activities is provided by contributions from partners (254). Sao Tome & Principe had a diplomatic relationship with Taiwan (1997-2016), having Taiwan implemented several projects, particularly in the areas of health, agriculture, and education (239). The Popular Republic of China, a country that had supported STP independence struggle and the post-colonial government in 1975, returned to establish health cooperation with STP in 2017 (239, 254). Cuba is also a country that has a health protocol with STP, sending teams of Cuban medical doctors, specialists in different fields, for long-term missions (approximately three years) at HAM (254).

Furthermore, STP also has a strong partnership and a health cooperation with Portugal. Portugal receives approximately 200 patients/year from STP due to the lack of some basic important techniques in this resource-constrained country, namely, haemodialysis treatment, cardiology interventions, and oncology treatments, among others (254). In the

last twenty years, the development of a Portuguese nongovernmental health project from Instituto Marquês de Valle Flôr, upgraded community-based health care and facilities, and recently scaled-up hospital resources with a telemedicine platform (general digital scanning, dermatology, ophthalmology, otorhinolaryngology, gastroenterology), allowed significant improvements in the delivery of health care in STP as well as providing equipment such as computerized tomography scan, mammography, and ultrasound at the HAM (244).

Nonetheless, it is still a country with very restricted and limited laboratory diagnostic tools (254). For instance, there are no culture techniques available (blood cultures, urine, spinal fluid and others), meaning that there is a major constraint in establishing diagnosis and bacterial and fungal identification and their resistance patterns (254). Another main problem is the lack of medicines as well as human resources, with 23 health professionals per 10.000 population (254). The national staff in 2017 consisted of 1338 health professionals, namely, 413 nurses (40 graduates and 10 specialists), 87 medical doctors (15 specialists), 200 diagnostic support technicians (30 graduates and 5 specialists), and 100 administrative technicians (40 licenced and 5 specialists) (254). The country has no means of graduating medical doctors (254). National students need to undergo medical university studies in countries such as Russia, Mozambique, Portugal, and Cuba (254). When they return to Sao Tome & Principe, they have basic training and are included in different departments for specific training in a specific field (254).

Due to these health constraints and ancient cultural beliefs and practices, it should be acknowledged that the population frequently seeks traditional medicine healers (255). According to the WHO, traditional medicine is defined as the combination of knowledge and practices used in the diagnosis, prevention, and elimination of physical, mental, or social diseases and is based on past observations and experiences transmitted from generation to generation (242, 255). Traditional medicine is seen both in STP and in many other countries alike, as something accessible and aimed at people of low economic power, it´s an acceptable reality and most population as his own healer or "*curandeiro*" (255). Practitioners of traditional medicine in STP usually have a reasonable working knowledge of ethnobotany and the composition of bush remedies, and this knowledge is

part of the culture of Sao Tome & Principe (255). Approximately 60% of the population makes use of healers and ancient traditional medicine (255).

1.6. Hospital Dr. Ayres de Menezes Maternity Unit

Hospital Dr. Ayres de Menezes (HAM), as previously mentioned, is located in the capital city, and is the reference hospital for the entire country, providing secondary and tertiary health care (254). It is also the teaching hospital for the training of newly graduated health technicians and nurses. The availability of inpatient beds at the referral hospital is 6/1000 inhabitants (254).

Each year, 82.4% of all deliveries occur at HAM, representing 4 500 babies born at the HAM maternity unit, approximately 13 deliveries per day (254, 256, 257). HAM maternity unit activity is also based on gynaecological health care, including outpatient consultations, scheduled gynaecological surgeries, emergency surgical procedures, gynaecological ultrasounds, and follow-up of oncological patients (254).

The HAM maternity unit is equipped with 58 beds, 2 delivery rooms with 6 beds, 3 dilation rooms, 1 operating room and 12 wards, 5 for puerperal women, 1 for infected surgery, 1 for special care, 1 for postsurgery, 2 VIP (very important inpatient) wards and 1 gynaecology ward. It works with an occupancy rate of 100%, with visits and daily consultations, every day of the week, including Sundays and holidays, serving approximately 60 patients daily (254). The maternity service comprises the following staff: 1) five obstetricians-gynaecologist (specialist doctors), four of whom are nationals, one from Chinese cooperation, who do not deal with emergencies and only work from 8 am to 1 pm; 2) four general practitioners; and 3) two medical assistants (254). There are 33 nurses, including the Head Nurse of the Service Department and 14 medical action assistants. Currently, there is only one anaesthesiologist working in STP (254). Health professionals (midwives or obstetricians) at HAM maternity assist in delivery, as per the WHO recommendation. Midwives are the main providers of maternity care (254).

The HAM maternity unit receives complicated cases referred from facilities in lower levels of care, as it is the only facility with Comprehensive Emergency Obstetric and Neonatal Care (CEmONC), that is, the only unit capable of providing blood transfusions and performing caesarean sections in the country, as already mentioned (254).

2. Health information and indicators

2.1. Sources and surveillance system in Sao Tome & Principe

Sao Tome and Principe have recently made progress in improving their vital registration and health surveillance systems, but there are still some challenges (236-238, 254). According to the WHO, the country has a civil registration system that covers the entire population and is decentralized, with registration offices in each district but is not considered to have a "complete registration" CRVS (242). The completeness and accuracy of vital statistics data is still a concern, as there are issues with underreporting, incomplete data, and delays in registration (254).

Data on neonatal and perinatal mortality in Sao Tome & Principe originate mainly form household sample survey programs that are conducted in the country, the UNICEF Multiple Indicator Cluster Survey Series (MICS), and the USAID-DHS (211). The measurement approach is slightly different between the two programs; subsequently, MICS and DHS surveys can present different results for similar indicators (211, 212).

In the MICS survey, mothers or caretakers of children in the household are typically the respondents, and the populations covered are children and women aged 15-49 (256). Neonatal data are collected from women who had given birth in the two years prior to the survey, an important limitation considering that data are subject to recall error (256). Moreover, surveys estimating neonatal/infant/child deaths require large samples because households in which a birth has occurred during a given year cannot ordinarily be preselected for sampling (212). The disclosure and limitation from MICS are added as follows: "unreliable estimate due to small sample size" (256).

Additionally, there are imprecisions in the causes of neonatal deaths reported (256). As an example, stillbirths and low birth weight (a complex clinical entity involving intrauterine growth restriction and prematurity) are not included in STP´s UNICEF MICS illustrating the gap in the knowledge of the country, adding to the diagnostic shortcomings on other causes, such as neonatal sepsis and the health service-related resource-constraints previously discussed (256).

2.2. Maternal and Child Health indicators

The evolution of the main maternal, neonatal and child health indicators in the period from 2009 to 2019 is describe in Table 3.

Table 3 | Evolution of the main reproductive, maternal, neonatal and child health indicators in the period from 2009 to 2019, Sao Tome & Principe

Indicator	DHS, 2009	MICS, 2014	MICS, 2019
Maternal Mortality Ratio	158/100 000 LB	74/100 000 LB	73/100 000 LB
Neonatal mortality rate	18/1000	22/1000	9/1000
Infant mortality rate	38/1000	38/1000	12/1000
Mortality rate in children under5	64/1000	45/1000	17/1000
Pregnancy rate among teenagers	22,8%	27.3%	21.9%

Abbreviations: LB_ livebirths

Sources: Data from Sao Tome & Principe USAID- DHS, UNICEF MICS 2014 and MICS 2019 (242, 245, 256).

2.3. Maternal mortality rate

Maternal mortality has been decreasing substantially in recent years. As already discussed, there are also various rates for maternal mortality rates according to different sources. For example, the Gates Foundation presents a higher rate (116 in 2020) than UNICEF (73 MMR in 2019) (240, 256). Nonetheless, STP has a lower rate compared to the other PALOP countries, such as Guinea-Bissau with 457 maternal deaths per 100 000 livebirths, Mozambique with 206, Equatorial Guinea with 181 and Angola with 167. Cape Verde had a lower rate of 43 maternal deaths per 100 000 livebirths (239).

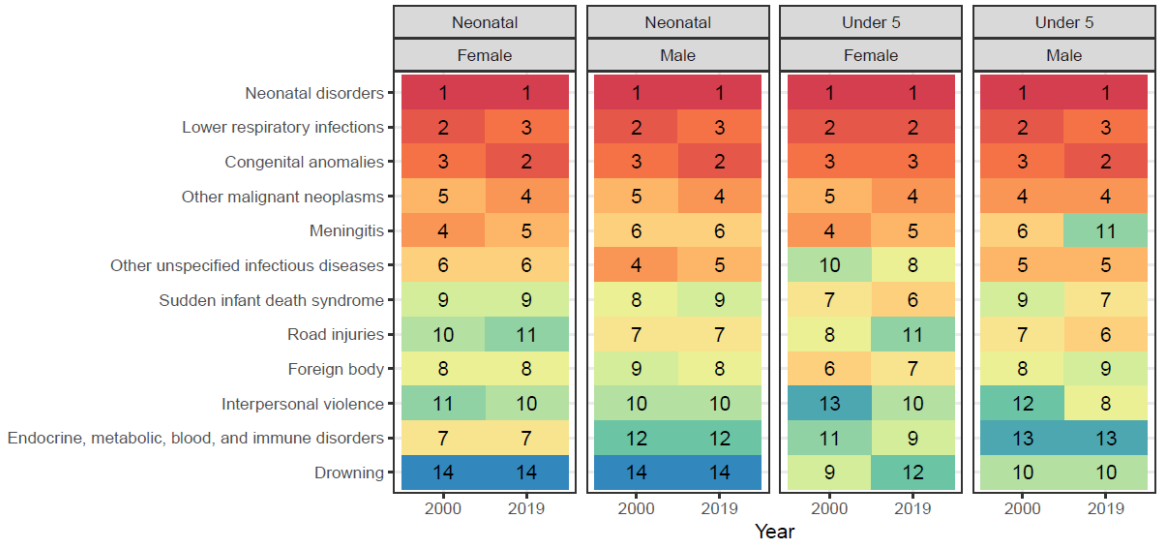
Several factors contributed to this reduction in STP, including the combination of service delivery and system strengthening measures, increased number of assisted births, maternal death audits, improvement of the referral chain to the community level, creation of obstetric care facilities of functional emergency, and several campaigns to sensitize women to go to the health centres closest to their area of residence (242, 246, 254).

2.4. Under5 mortality rate

Child mortality rates have steadily decreased in the past 15 years (240). The mortality rate in children under5 years old diminished from 64 in 2009 to 17 per 1000 livebirths (239).

The main causes of death for the under5 causes for Sao Tome & Principe, comparing 2000 and 2019, are described in Table 4.

Table 4 | Main causes of death for the neonatal period and under5 causes for Sao Tome & Principe, comparing 2000 and 2019 (estimations), according to sex.



Legend: 1 indicates the highest probability of cause of death, and 14 indicates the lowest probability.

(Image source: from Supplement to: Global, regional, and national progress towards Sustainable Development Goal 3.2 for neonatal and child health: all-cause and cause-specific mortality findings from the Global Burden of Disease Study 2019, Lancet 2021 (8), https://doi.org/10.1016/S0140-6736(21)01207-1_licensed under CC BY 4.0)

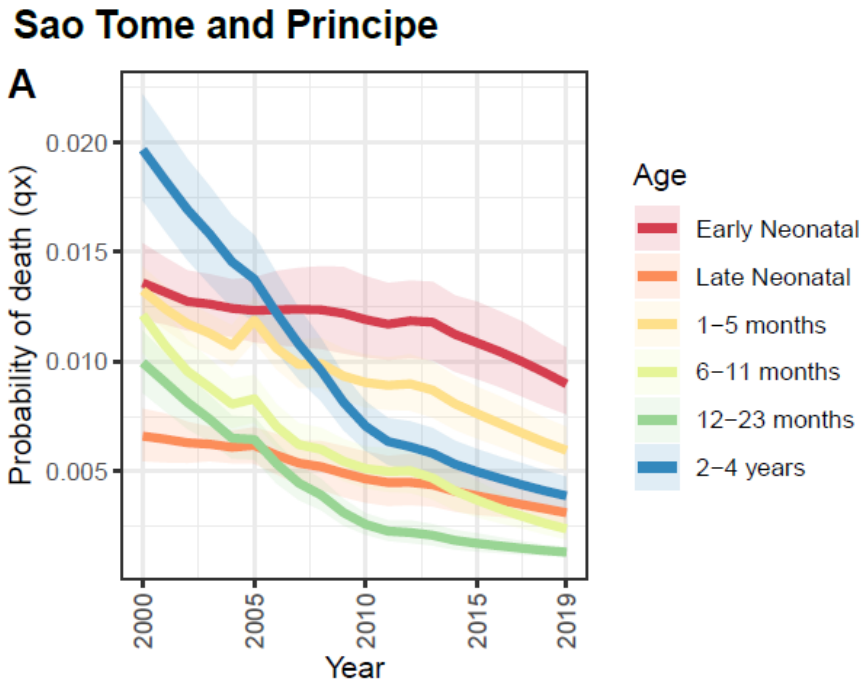
Moreover, this reduction in the U5MR can be attributed in part to the results of vaccination, whose coverage for the main antigens (BCG, DTCP3 and VOP3) increased by more than 80% compared to the year 2000 (242, 246). Currently, national coverage is mainly ensured by the routine vaccination of children under one year of age against tuberculosis, tetanus, whooping cough, poliomyelitis, and rubella (242). Hepatitis-B and yellow fever were integrated in 2003 and Hib (pentavalent vaccine) was integrated in 2009 (245). As part of the introduction of the new vaccines, with a great impact on the U5MR reduction, was the introduction of the pneumococcus vaccine (PCV-13) in November 2012, the second dose of measles in 2013, and the VPI and rotavirus vaccine in 2016 (245). Only in October 2016, did the introduction of the combined measles/rubella vaccine begin (245, 246).

In addition to immunization, two other measures contributed to this reduction in the U5MR in STP, namely, a reduction in malaria cases and the implementation of the childcare strategy Integrated Management of Neonatal and Child Illnesses (IMNCI) (240, 246). IMNCI refers to a broad WHO/UNICEF initiative that was launched globally in 1995 with the objective of reducing under5 mortality, morbidity, and disability and improving child growth and development (246).

Moreover, access to treatment for the main childhood illnesses and the practice of exclusive breastfeeding is good, which has also contributed to the reduction of infant mortality rates (240, 246). Even during the pandemic years, all health units in the country continued offering IMNCI, and the number of children with pneumonia treated with antibiotics increased from 1290 in 2020 to 1635 in 2021 (36, 257).

Neonatal deaths in STP account for approximately 48% of all under5 deaths, and early neonatal deaths are the main causes of under5 child deaths in STP (Chart 2) (258). Nonetheless, the neonatal period is the most vulnerable in STP.

Chart 2 | Probability of child under5 death according to specific age subgroups between 2000 and 2019 in Sao Tome & Principe



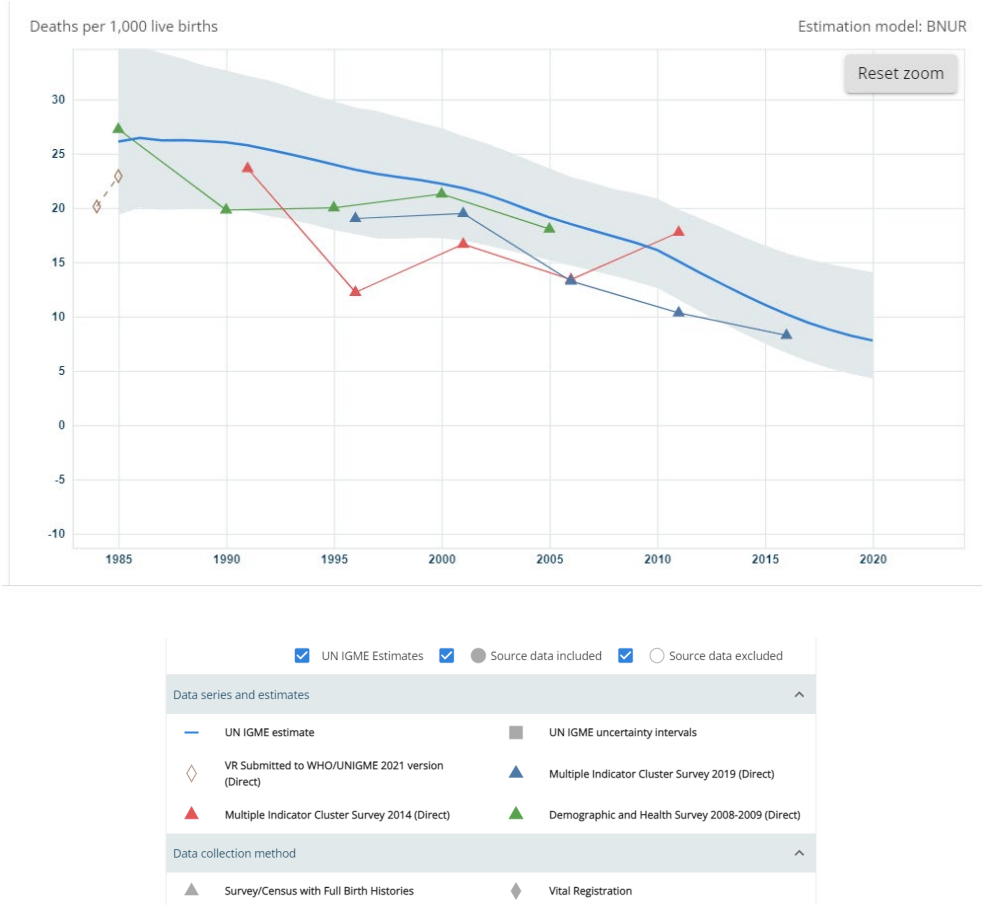
(Image source: from Supplement to: Global, regional, and national progress towards Sustainable Development Goal 3.2 for neonatal and child health: all-cause and cause-specific mortality findings from the Global Burden of Disease Study 2019, Lancet 2021 (8), https://doi.org/10.1016/S0140-6736(21)01207-1 licensed under CC BY 4.0)

2.5. Neonatal mortality rate and stillbirths

Neonatal mortality increased between 2009 and 2014 (Table 4) and decreased recently (246).

For 2020, the UN IGME uncertainty interval is 4.34 to 14.53 neonatal deaths per 1000 livebirths (Chart 3), and the stillbirth rate UN IGME uncertainty interval is 5.5 to 14.67 stillbirths per 1000 livebirths (10).

Chart 3 | Differences in neonatal mortality rates in Sao Tome & Principe according to different sources (deaths per 1000 livebirths)



Legend: UN IGME uncertainty interval is 4.34 to 14.53 (2020). How to read this chart instructions available in Appendix 6.

Source: Estimates developed by the UN Inter-agency Group for Child Mortality Estimation (UNICEF, WHO, World Bank, UN DESA Population Division). 2021. (10) Available from: http://childmortality.org.

Causes for neonatal deaths in the country are estimated to be due to prematurity (46%), intrapartum birth asphyxia and trauma (21%), and congenital malformations (8-14%) (258).

It should be acknowledged that the rates available are only estimations and can be associated with underreporting (258). As may be observed in Chart 4, different data sources estimate different rates for neonatal deaths and stillbirths in STP for the same period, reinforcing that the methodologies used only allow to have a general view of the problem.

2.6. Adverse birth outcomes

A prevalence of 12% (8.6 – 16.7) PTB and 6.6% (5.0-8.6) LBW was published in 2019, estimated from a global modelling analysis (80).

Missing data: There is data concerning prevalence, morbidity and types of congenital anomalies detected in the country. Moreover, there are also no studies or reports estimating neonatal sepsis. There are also no specific rates for intrapartum conditions among newborns in STP.

Prior to 2010, there was a total lack of neonatal resuscitation material in STP maternities, and midwives had low skills to help newborns transition to extrauterine life (244, 259). Between 2010 and 2012, an intervention project of newborn resuscitation, support delivery and alarm signals in the first months of life was implemented in STP (Appendix 7) (259). The project included theoretical and practical hands-on-training of 110 health professionals (100 midwives) from around the country and equipping the countries' seven maternity units with neonatal material for resuscitation (259).

3. Associated factors

Factors associated with the main adverse birth outcomes and peri-neonatal mortality known for Sao Tome & Principe will be addressed next, according to the factors considered for this thesis described in Part I and Figure 6.

3.1. Maternal Factors

Age: Adolescent pregnancy and early motherhood are major public health issues in the country (Table 3) (246, 247). The adolescent fertility rate (births per 1000 women aged 15-19) is estimated to be 94.8 ‰ for STP (260). This proportion is higher when compared to Cape Verde (72‰), but significantly lower than other PALOP countries, such as Angola (145‰), Mozambique (144‰) and Guinea-Bissau (102‰) (260).
Regarding child marriage, 5.4% of girls married before achieving 15 years and 28% before 18 years old (240, 256).
Pregnancy in elderly pregnant women (prevalence and adverse outcomes) is unknown.

Education: There is a 75.7% literacy rate of women and 60% secondary education completion rate (257). One of the country constraints is that only 29.2% of teachers have adequate training as the remaining 63.2% are untrained and lack specific skills (247).

Family support: The main structure is the existence of nuclear-type families formed by the couple and their children (261). MICS-STP 2019 reports that 20.3% of women are in a polygamous union (256).

Employment and economic independence: Women are mostly unemployed and constitute most of the inactive population, representing approximately twice as many men in the same situation, that is, 66.5% of women versus 33.5% of men (256). Poverty affects relatively more women (71.3%) than men (63.4%) and seems to be negatively correlated with the level of education (236, 241).

Living conditions: Houses are typically small wooden built under stilts and with a metallic zinc roof, 80.8% of households use two divisions to sleep, and 10.6% of families live in houses with a single accommodation division (261). Approximately 77.2% of household members use improved drinking water sources in their home/garden/yard or within 30 minutes and 20% are deprived of access to water (256). Regarding sanitation, 18% of households have a bathroom, and 24.7% use latrines with open defecation, estimated to be 42.7% in urban areas and 51.1% in rural areas (261). Concerning the kitchen, 71% of households have one (43.2% outside the house and 27.8% within the accommodation). Firewood is the main type of fuel for cooking, followed by oil (261). Approximately 65% of urban households have electricity (43% rural), 25% households have a fan, 2% have air conditioning and 2% of households have a washing machine (256).

In terms of communication, 67.1% of women aged 15 to 49 years old have a mobile phone, and only 8.9% use it (256).

3.2. Preconception factors

Reproductive Health Program: The National Reproductive Health Policy provides the delivery of free family planning services in all the health centres in the country (247). There is a National Strategy for Adolescent and Youth Health and a Strategic Plan, that is available at all health facilities (247). The Reproductive Health Centre in Água Grande is the only one that provides an exclusive space for adolescent reproductive service (247). The policies, strategies and plans related to reproductive, maternal, newborn, child, adolescent, and nutrition (SRMNEA-N) health developed in the context of MDGs were kept and reinforced with the SDG era (247).

Contraceptive use: According to MICS 2019, 49.7% of women used a contraceptive method, either modern or traditional (rhythm, withdrawal, calendar) (256).

Sexual debut: In a study carried out in 2001, approximately 20% of young people under the age of 17 already had an active sex life and knew the risks of unprotected sex (262).

A high incidence of voluntary termination of pregnancy and abortion outside the hospital system in 37.5% of women aged between 15 and 17 years old was reported (262).

Preconception: Data concerning parity, previous stillbirth, PTB and LBW, interpregnancy interval, supplementation, chronic diseases, and type of pregnancy planning among pregnant women in the country were not found.

3.3. Antepartum factors

Antenatal care coverage: The country reached high ANC coverage; 98.1% of women are attended at least once by a skilled health provider during pregnancy, 12.8% of women attend at least four ANC contacts and 4.3% of women attend at least eight ANC contacts (256).

Since 2017 there has been a recommendation for a minimum of eight ANC contacts during pregnancy, replacing the previous FANC model of four ANC visits (246).

ANC contacts are carried out by nurses on all working days in all district health centres (246, 247). Procedures follow the WHO manual on "Integrated Management of Pregnancy and Childbirth Managing Complications in Pregnancy and Childbirth: a guide for midwives and doctors" (246, 247).

Pregnant women´s care during the ANC period is recorded in a booklet that is usually referred to as an ANC pregnancy card, which is an important working tool. It has ten pages and health workers use it as continuous documentation for pregnant women registering personal information, physical examinations, laboratory tests, treatments, and other notes (Appendix 12). Pregnant women bring the card to each visit and carry it to the maternity unit at the time of delivery.

ANC screenings: Approximately 91.7% of women reported that during the pregnancy, at least once, they had blood pressure measured and gave urine and blood samples as part of antenatal care (256).

ANC screening tests are performed according to the 2016 WHO recommendations (139). Screening of human immunodeficiency virus (Determine© test), hepatitis B virus

(hepatitis B surface antigen - HBsAg) and syphilis (rapid plasma reagin test) are included in the essential package of interventions for maternal and newborn health, which is done using an opt-out approach and is free of charge (Table 5) (246, 247). Interventions such as tetanus toxoid immunization, intermittent preventive treatment for malaria during pregnancy (IPTp), and insecticide-treated bed-nets are also provided without costs (246, 247). Urine culture is not available in STP, so urine dipstick tests in health posts and laboratory urine in other centers are the methods used (246, 247). Additionally, as full blood count testing is not available in most district units, on-site haemoglobin testing is performed with a haemoglobinometer (246, 247). Full blood count testing (gold-standard) is only available at HAM (246, 247). ANC contacts are free, but women pay approximately USD$6.7 for all mandatory tests, such as blood, urine, stool, and gynaecological exams, plus USD$10 for obstetric ultrasounds that are mainly available at private obstetricians' clinical facilities (246, 247).

ANC maternal problems: There is a 61% prevalence of anaemia in pregnant women (246). Data concerning gestational diabetes mellitus, hypertension, maternal haemorrhage, Rh and ABO incompatibility prevalence were not found.
Infectious conditions that affect pregnancy and maternal immunization were previously described in section 1.4. Part III and are summarized in Table 5.
No data concerning TORCH, bacteriuria or *group B streptococcus* colonization or infection were found.

3.4. Intrapartum factors

Skilled maternal health care: Skilled birth attendance reached a 96.8% rate in 2019 (256). Approximately 95.4% of all deliveries occur in maternity units, mainly (82.4%) at the HAM maternity unit (256).

Childbirth/delivery in the rural districts: Each district has one maternity ward located at the district health centre for uncomplicated deliveries, which is responsible for less than 20% of all country deliveries. Cantagalo is the only district of the country that does not have a maternity ward. These maternity units are also classified as BEmONC (section

2.4.1. Part I) (246, 254). Currently, Lembá, Lobata, Caué, Me-Zochi, and Principe Island have the capability of performing obstetric ultrasounds (254). Nonetheless, district maternities are not fully capable of some competencies, such as manual intrauterine aspiration, suction cup application during delivery and product extraction intrauterine residuals after abortion (246, 254). Therefore, all pregnant women or newborns with complications must be referred to HAM at the city capital (254). The time to travel and distance between the basic district maternity units and the main HAM can take up to two-three hours, according to the weather condition. In the case of Principe Island, pregnant women need to be transferred by airplane, reaching 24 hours to be transported, although the flight takes half an hour to travel between Principe Island and Sao Tome Island.

Table 5 | Infectious conditions among pregnant women in Sao Tome & Principe

INFECTIOUS CONDITIONS	
MTCT of HIV	3.18% MTCT of HIV (2016) to zero cases of MTCT of HIV (2021)
MTCT of syphilis	syphilis in pregnant women decreased from 1.8% (2008) to 0.8% (2017) no cases of congenital syphilis (2008 -2017)
MCTC of hepatitis B virus	6.1% seroprevalence HBsAg in women universal newborn HepB-BD vaccination without maternal screening (2018)
Malaria	26 pregnant women had malaria (2021)
Intestinal parasitic infections	unknown prevalence of IPIs among pregnant women Country is endemic for STH (70%) and *S intercalatum* (7.6%)
Neonatal Tetanus	zero cases Maternal and neonatal tetanus elimination status for STP
Maternal immunization	Tetanus for pregnant women (routine VAP) (1977) Replaced by the Td (Tetanus/diphtheria) vaccine (2013) Introduction of combined measles/rubella vaccine (2016)

Sources: Data abstracted from references (242, 245, 246, 247, 257).

Emergency obstetric care: The HAM maternity unit receives complicated cases referred from facilities in lower levels of care, as it is the only facility with Comprehensive

Emergency Obstetric and Neonatal Care (CEmONC), that is, the only unit capable of providing blood transfusions and performing caesarean sections in the country (254).

Obstetric complications: There is a paucity of locally generated evidence on the magnitude of obstetric complications among pregnant women in STP. No study or report was found regarding the prevalence of major obstetric haemorrhage, preeclampsia/eclampsia, obstructed labour, prolonged rupture of membranes, meconium-stained amniotic fluid, or other intrapartum factors.

3.5. Postpartum Factors

Essential immediate newborn care: The rates of babies who are placed on the mother's bare chest after birth are 29.2% and early breastfeeding is achieved in 35.7% of cases (256). Approximately 75.9% of the newborn's first bath is delayed more than 24 hours after birth, as recommended by the WHO (256). Neonatal screening available is mostly related to clinical examination. Babies are routinely screened for deafness, but not for heart defects or abnormalities of the thyroid or adrenal glands before discharge from the maternity unit (244).

Recently, the UNICEF supported the MoH in updating the national breastfeeding policy and implementing the Baby Friendly Hospital Initiative in the six maternity units in the country with the aim of ensuring adequate newborn nutrition through breastfeeding exclusivity (257).

Emergency neonatal care package: There is only one basic Neonatal Care Unit (NCU) at the HAM (254, 259). It has six baby cots, and the management of common neonatal problems is generally performed according to the WHO guidelines available at the "Pocket book of hospital care for children: guidelines for the management of common illnesses with limited resources" (205).

Although NCU was rebuilt in 2016, there is still a lack of continuous positive airway pressure therapy, surfactant therapy and enteric feeding for assisting sick babies. There is no essential microbiology technique investigation, making it impossible to know which microorganisms are involved in neonatal sepsis or other infections in the country (254).

To highlight the inexistence of neonatologists in the country, the NCU is coordinated by two general medical doctors (254). The NCU has two nurses scheduled between 07:30 am and 01:00 pm from Monday to Sunday. For the period between 01:00 to 04:00 pm and 04:00 pm to 07:30 am, there is one nurse scheduled (254).
There are no previous studies regarding the number and causes of neonatal admissions at this unit.

Postnatal care: The first opportunity for postnatal service is at the hospital or at the district maternity units (246). Approximately 92.3 % of women reported attending health facilities for newborn postnatal care at least once within 42 days after delivery, 84.1 % of whom were also observed (256).

Part IV | Thesis Aim and Objectives

1 | Rationale

Sao Tome & Principe has no scientific information on neonatal health, mortality, stillbirths, adverse birth outcomes and associated factors, as far as acknowledged. As a result, there is an unmet need for studies on this subject.

Accurate reporting on neonatal mortality rates and causes is still lacking. Thus, the true magnitude of stillbirths, perinatal and neonatal deaths in STP is unknown due to the invisibility of the newborn child in policies and statistics.

The consequences of inaccurate data and poor understanding of the problem can be detrimental to improving neonatal health; based on 'what is measured influences what is done', measurements, causes and associated factors need to be studied in this country in order to ensure proper allocation of resources and to target interventions based on scientific evidence (208).

Factors associated with neonatal outcomes can be similar among the sub-Saharan Africa region, but the huge diversity of each country does not allow the making of assumptions and different contexts and heterogeneity of maternal and neonatal health determinants can bias the precise quantification of the contribution of each factor (223, 263).

Taking that into account, it is highly important to have country-specific data for making the right decisions; the number of perinatal and neonatal deaths, types of frequent adverse birth outcomes and main associated factors are key to determine which are the target high-impact solutions for this setting.

Therefore, the objectives of this thesis are to answer the triple *Wh* question *When, Where and Why* do newborns not only get sick but also die in Sao Tome & Principe, through the analysis of causes and risk factors contributing to perinatal and neonatal morbidity and mortality in this resource-constrained country.

The HAM maternity unit was selected purposely for this study as it is responsible for more than 80% of all deliveries in the country, providing an opportunity in this research to include pregnant women living in different districts, and to therefore obtain a better global picture of the country. Additionally, women carry their ANC pregnancy card to the maternity ward, providing an opportunity to check ANC practices and screenings from all country districts. It also enables access to data on the most frequent adverse birth outcomes (prematurity, intrapartum conditions, sepsis, and congenital anomalies), mortality, and of the overall identification of intrapartum, postpartum and healthcare service-related main associated factors.

Adolescent pregnancy, as previously mentioned, is identified as a major public health concern in STP. Mothers and newborns health are inextricably bound; thus, the characteristics and factors amongst adolescent pregnant women and their impact on neonatal outcomes will also be studied.

STP no longer faces the previously intense burden of malaria and MTCT of HIV, syphilis, and HBV is about to be eliminated, but the impact of other infections, namely, bacteriuria and intestinal parasitic infections (IPI) among pregnant women and their offspring, is unknown. A gap in ANC coverage rate and screening tests completion has also been perceived and were aimed to be analysed through this research.

Additionally, there is also a paucity of data regarding intrapartum factors mainly obstetric complications among pregnant women delivering at HAM, emphasizing the need for studies in this field.

Thus, this PhD research findings will add to the current evidence of maternal and neonatal health in Sao Tome & Principe and will support the design of targeted interventions and better allocate resources to where they are needed.

2 | Aim and Objectives

The general aim of this thesis is to identify maternal, preconception, antepartum, intrapartum, and postpartum associated factors and to determine whether they may be associated with newborns morbidity and mortality, including stillbirths.

Primary objectives

- To identify the most vulnerable period for death (partum, early neonatal, and late neonatal period).
- To identify where newborns die (in the maternity, at home or in the paediatric ward).
- To identify the main factors associated with death outcome.
- To identify the main adverse birth outcomes and associated factors.
- To study measures to overcome these situations in collaboration with local political decision-makers.

Secondary objectives:

- To determine whether adolescent pregnancies contribute to adverse birth outcomes and to identify factors associated with early motherhood in STP.
- To acknowledge the current ANC practices in the country and to identify maternal determinants for an adequate ANC service utilization.
- To determine whether intestinal parasitic infection is associated with adverse birth outcomes and to identify main associated factors.
- To understand the level of knowledge that mothers have regarding neonatal danger signs.

The thesis objectives and their corresponding articles are described in Table 6.

Table 6 | Thesis objectives and corresponding articles (I, II, III and V) and manuscripts (IV, VI, VII and VIII)

PRIMARY OBJECTIVES	Articles/Manuscripts
Perinatal and neonatal mortality To identify the most vulnerable period for newborns death (partum, early neonatal, and late neonatal period). To identify where newborns die (in the maternity, at home or in the paediatric ward). To identify the main factors associated with newborn death outcome.	VIII - Factors associated with perinatal and neonatal mortality in Sao Tome & Principe: a prospective cohort study
Adverse birth outcomes To identify the main adverse birth outcomes and associated factors	VII - Adverse birth outcomes and associated factors among newborns delivered in Sao Tome & Principe: a case–control study I - Adolescent pregnancy in Sao Tome & Principe: are there different obstetric and perinatal outcomes? VI - Intestinal parasitic infections and adverse outcomes among pregnant women and their newborns in Sao Tome & Principe: a hospital-based cross-sectional study
SECONDARY OBJECTIVES	
Maternal factors To determine whether adolescent pregnancies contribute to adverse birth outcomes and to identify factors associated with early motherhood in STP.	I - Adolescent Pregnancy in Sao Tome & Principe: a cross-sectional hospital-based study II – Adolescent pregnancy in Sao Tome & Principe: are there different obstetric and perinatal outcomes?

Antepartum factors: Antenatal care To acknowledge the current ANC practices in the country and to identify maternal determinants for an adequate ANC service utilization.	III - Antenatal screenings and maternal diagnosis among pregnant women in Sao Tome & Principe – missed opportunities to improve neonatal health: a hospital-based study IV - Determinants of antenatal care utilization – contacts and screenings – in Sao Tome & Principe: a hospital-based cross-sectional study
Antepartum factor: Instestinal parasitic infection To determine whether intestinal parasitic infection may be associated with adverse birth outcomes and to identify main associated factors.	V – Intestinal parasitic infections, treatment, and associated factors among pregnant women in Sao Tome & Principe: a cross-sectional study VI - Intestinal parasitic infections and adverse outcomes among pregnant women and their newborns in Sao Tome & Principe: a hospital-based cross-sectional study
Mother´s knowledge of neonatal danger signs To understand the level of knowledge that mothers have regarding neonatal danger signs.	II - Adolescent Pregnancy in Sao Tome & Principe: a cross-sectional hospital-based study
Policy implications and recommendations Measures and interventions to be discussed with the Ministry of Health, stakeholders, and the scientific community in their work to reduce preventable neonatal mortality, stillbirths, and ABOs in STP.	- Every article and manuscript have specific recommendations - Recommendations will also be present in the thesis discussion and conclusions (section 4 Chapter 4). - Sao Tome & Principe MoH and health care professionals from HAM will have access to paper's summaries through a Portuguese translation. Additionally, a presentation will be performed in a meeting organized to address neonatal and pregnant women health in the country. - Policy Implications: two projects were elaborated and submitted for funding to improve neonatal care unit in the country (Appendix 2 and 3). - Two additional research projects are being conducted/prepared to identify main gaps on neonatal postpartum care in the country (Appendix 4 and 5).

Part V | Chapter 1 References

Chapter 1 References

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Chapter 2 |

| Material & Methods

Material and methods will be only briefly presented in this chapter since this is a "research-paper-style" PhD thesis (detailed description in Chapter 3).

This thesis involves eight articles/manuscripts which are all interrelated and complement each other. Table 7 presents the summary of the main material and methods that were common to these articles/manuscripts. Since the case-control study supported the thesis protocol approval and FCT grant it will be briefly described next.

Study design: quantitative, analytical, observational, unmatched case-control study (complementary information included in manuscript VII).

Setting: Hospital Dr. Ayres de Menezes (HAM) is the only hospital on Sao Tome Island, with a maternity ward delivering approximately 82.4% of all deliveries in the country with an average of 8 to 12 deliveries per day (4500 births per year) (described in section 1.6. Part III, Chapter 1).

The number of deliveries at the hospital was considered to be broadly representative of the population of newborns in the country. The HAM maternity unit was the source of cases and controls.

Population: Newborns in Sao Tome & Principe. The study population included newborns (mother-neonate dyads) admitted to the HAM maternity unit during the study period.

Main outcome measures: identification of the main causes and characteristics of neonatal disease and the pattern of perinatal and neonatal mortality. Adjusted odds ratio estimates for maternal, antepartum, intrapartum, and postpartum associated factors.

Table 7 | Summary of this PhD research materials and methods

Methods	Description
Study design	This PhD research included: Cross-sectional study (article/manuscript I, II, IV, V and VI) Retrospective chart review (article III) Case-control study (manuscript VII) Prospective cohort study (manuscript VIII)
Setting	Hospital-based study: HAM maternity unit at Sao Tome & Principe. Maternity ward delivering around 82.4% of all the deliveries in the country with an average of 8 to 12 deliveries per day (4500 births per year).
Recruitment period	Between July 2016 and November 2018. The recruitment was done at different months: two to three weeks every two other months. A total of 150 days for the field recruitment. A medium of 3 to 4 participants were recruited per day (2 to 3 hours per participant for completion of all data abstraction and face-to-face interview).
Participants	All pregnant women admitted to the HAM maternity unit for delivery constituted the source population, whereas the study population included selected pregnant women admitted to the HAM maternity unit during the study period. For the studies on articles/manuscripts II, VI, VII and VIII the newborns or mother-birth-dyads were included.
Eligibility criteria	The eligibility criteria for participants were: 1) prepartum women admitted to the HAM maternity unit for delivery with a gestational age of 28 weeks or more 2) prepartum adolescents (under ≤ 19 years and with a GA ≥28 weeks) and illiterate women who had obtained permission from their parent/s or legal guardian/s to participate in the study and 3) women and adolescents who gave birth outside the hospital but were admitted for postpartum care on the day of birth (newborn with ≤12 hours of life). From the initial 534 eligible prepartum women that consent to participate in this PhD research, 16 were excluded since they were discharged from HAM maternity unit before conducting the face-to-face interview. Exclusion criteria for each study described in Table 8.
Total participants	**518 mothers** (prepartum women who consented to participate) **535 newborns** (34 twins) or 535 mother-birth-dyads

Randomization	A random sampling was applied to recruit the study participants until the required sample size was achieved. Participants were invited to participate in the study after admission to the HAM maternity unit. Each morning from Monday to Friday, from the pile of medical folders from the prepartum women admitted for delivery, every second interval folder was selected and then carry on asking the participant the consent for enrolment.
Variables	Variables´ definitions are described in each article/manuscript. The operationalization of the variables used in this research can be consulted on Appendix 8.
Data sources	Data on antepartum, intrapartum, and postpartum characteristics of participants, were gathered and collected from 1) ANC pregnancy cards, 2) obstetric maternal hospital records 3) newborns' records. Maternal sociodemographic and preconception data were obtained through a face-to-face interview of the mothers, using a structured questionnaire (Appendix 8). The questionnaires were performed in Portuguese, the national language. Women's consent to participate in the study was obtained at the time of admission at HAM, but the face-to-face interview was held after a woman was stabilized and ready to be discharged.
Investigator role	The PhD researcher executed and was responsible for all main field activities, namely: 1) obtaining consent and enrolment of the participants, 2) data collection from ANC pregnancy cards plus maternal clinical and newborn's records, 3) newborns` clinical exams (for diagnosis confirmation), 4) face-to-face interviews with all mothers 5) conducting on-site-rapid-syphilis test (Hexagon Syphilis) (Appendix 9) 6) data collection entry into the app survey tool.
Study size	Sample size was calculated using the WHO-steps approach [45] using a web based freely accessible sample size calculator, Raosoft® (http://www.raosoft.com/samplesize.html). Based on the formula for sample size and margin of error from the software, the minimum sample size was S = 355, which placed the right dimension between 355 (95%) and 579 (99%) confidence. For the original study (manuscript VII), a total of 518 participants were enrolled based on the following assumptions: two-sided 95% confidence level, power of 80% to detect an odds ratio of at least 2 for adverse birth outcomes.

	This sample size was also supported by PASS® software (https://www.ncss.com/software/pass/).
Data management	Data were secured in a confidential and private location. Participants were referred to by identification numbers, and the informed consent forms were kept separate. Both could only be linked by a coding sheet available to the investigator.
Data quality control	The questionnaire was pretested at HAM one month before data collection in 23 mothers, and modifications were made based on the pretest results, mainly adjusting terminology for more culturally friendly terms. During the data abstraction period, supervision of data collection and continuous follow-up were made by the supervisors. The collected data were checked daily for completeness. The captured data was checked for completeness and accuracy by a qualified biostatistician.
Statistical methods I	Data collected were directly entered into QuickTapSurvey (2010–2021 Formstack) an offline survey app tool, and further analysis was conducted in the Statistical Package for the Social Sciences for Windows, version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).
Statistical methods II	**Articles/Manuscripts III and VI** Comparisons of groups were assessed using the Chi-squared test or Fisher's exact test. A level of significance α=0.05 was considered. **Articles/Manuscripts I, II and VIII** Univariable logistic regression analysis was used to estimate the unadjusted effect of each independent variable on the dependent variable. **Articles/Manuscripts IV, V and VII** Univariable analysis was applied to identify the candidate variables for the multivariable analysis (with a p value <0.25). Crude odds ratios (CORs) and adjusted odds ratios (AORs) with corresponding 95% confidence intervals (95% CI) were estimated.
Consent to participate	Written informed consent was obtained from all participants after the purpose of the research was explained orally by the researcher (Appendix 10). Approval by the participants' parents or legal guardians was asked in the case of adolescents under 16 years of age or illiterate women. The participants or their legal representatives also consented to have the results of this research work to be published. Participation in the survey was voluntary, as participants could decline to participate at any time during the study.
Ethics approval	Ethical clearance was obtained from the Democratic Republic of Sao Tome and Principe Ministry of Health and Hospital Dr. Ayres de Menezes (Appendix 11).

Table 8 describes each article/manuscript according to the study participants enrolled, exclusion criteria, study strategy, description, definition of subgroups (if the case), and data sources specific for each study.

Table 8 | Participants description and data sources used for each article/manuscript

Articles/Manuscripts	Study Participants	Exclusion Criteria	Strategy	Description/Subgroups	Sources*
I Adolescent pregnancy in Sao Tome and Principe: a cross-sectional hospital-based study	**518** mothers	1) adolescents <13 years 2) adolescents who had not obtained permission from their parent/s or legal guardians to participate in the study; 3) adolescents with cognitive impairment; and 4) those admitted for abortion (GA< 28 weeks). None meet the exclusion criteria.	Girls ≤19 years of age (n=104) were compared to adult mothers (n=414)	3 subgroups: 1) very early childbearing as birth before age ≤15 (n= 8), 2) early childbearing for birth between age >16 and ≤17 (n=45) 3) late childbearing for birth age >18 and ≤19 (n=51) were compared to the older women group	1 2 3
II Adolescent pregnancy in Sao Tome and Principe: are there different obstetric and perinatal outcomes?				Subgroup analysis of primiparas and multiparas	1 3 4
III Antenatal screenings and maternal diagnosis among pregnant women in Sao Tome & Principe – missed opportunities to improve neonatal health: a hospital-based study	**511** mothers	1) women with induced termination of pregnancy for medical reasons, 2) adolescent or illiterate mothers who had not obtained permission from their parents or legal guardians to participate in the study, and 3) women without an ANC card. 7 excluded for not having an ANC card	Retrospective hospital-based study in which ANC cards were reviewed	ANC screenings were described and compared according to the total number of ANC contacts: 1–3 (inadequate ANC) (n=76) 4–7 (adequate ANC) (n=237) ≥8 (complete ANC) (n=198)	1
IV Determinants of antenatal care utilization – contacts and screenings – in Sao Tome & Principe: a hospital-based cross-sectional study	**445** mothers	The exclusion criteria included 1), 2) and 3) from manuscript III plus 4) missing information of the timing of first ANC contact. 66 participants were further excluded in relation to manuscript III for missing information of the timing of first ANC contact	Women with an optimum ANC utilization (n=213) were compared to those with suboptimum ANC utilization (n=232)	Optimum ANC utilization was defined when pregnant women had all the following: 1) attended ANC clinic four or more times, 2) first booking before the 12th gestational week, 3) had at least one ultrasound, 4) had at least one urine test, and 5) performed no less than one haemoglobin test. Suboptimum ANC utilization included those who attended ANC clinic one or more times regardless of whether they had or	1 2

				not, an obstetric ultrasound, urine, or any haemoglobin test.	
V Intestinal parasitic infections, treatment, and associated factors among pregnant women in Sao Tome & Principe: a cross-sectional study	**361** mothers	1) pregnant women with GA <28 weeks, 2) women who had no ANC card, 3) pregnant women without an ANC copro-parasitological screening 4) pregnant women with HIV, sickle cell disorder, and malaria 5) women with cognitive impairment, 6) women who were unstable due to postpartum complications, 7) adolescent or illiterate mothers who had not obtained permission from their parents or legal guardians to participate in the study. Pregnant women without ANC copro-parasitological screening (n=147) and with HIV, sickle cell disorder, and malaria (n=10) were excluded	Pregnant women with an IPI (n=210) were compared to noninfected women (n=151)	For the anthelmintic prescription analysis, three different groups were considered since the recommended drugs are different for helminthiasis (albendazole, mebendazole, or piperazine), schistosomiasis (praziquantel), and amebiasis (paromomycin, plus metronidazole or tinidazole)	1 2
VI Intestinal parasitic infections and adverse outcomes among pregnant women and their newborns in Sao Tome & Principe: a hospital-based cross-sectional study			Pregnant women with a monoparasitic IPI (n=145) and polyparastic IPI (n=25) were compared to non-IPI (n=151) pregnant women for ABOs	IPI subgroups: 1) helminthiasis (n=162), 2) schistosomiasis (n=11) 3) amebiasis (n=7) were each compared to the non-IPI (n=151) group *40 pregnant women with helminthiasis infection were excluded from the ABOs analysis due to adequate anthelmintic drug ANC treatment	1 2 4
VII Adverse birth outcomes and associated factors among newborns delivered in Sao Tome & Principe: a case–control study	**519** newborns	1) all neonates delivered at HAM born without any signs of life (stillbirths), 2) newborns whose mothers had cognitive impairment, and 3) adolescent or illiterate mothers who had not obtained permission from their parents or legal guardians to participate in the study. 16 met the exclusion criteria (stillbirths)	176 cases and 343 controls (unmatched) were compared	Newborns with one or more ABO (GA <37 weeks, LBW < 2.5 kg, BW >4 kg, 5-minute Apgar score <7, major congenital anomalies, and probable sepsis based on clinical criteria) were the cases (ABO group), while healthy newborns without ABO were the controls (no-ABO group)	1 2 3 4 5
VIII Factors associated with perinatal and neonatal mortality in Sao Tome & Principe: a prospective cohort study	**194** Maternal-neonate dyads	1) all neonates delivered at HAM with a gestational age of less than 28 weeks, 2) newborns whose mothers had no ANC pregnancy card, 3) newborns whose mothers had cognitive impairment, 4) newborn health status unknown at the twenty-eight day of life From the 535 mother-neonate dyads, 341 were lost to follow-up (LTFU)	Maternal-neonate dyads were followed up after the 28th day of life (n=194). Neonatal death-outcome (n=22) and alive-outcome groups (n=172) were analysed and compared.	Subgroups: 1) stillbirths (n=16) 2) early neonatal death (n=4) 3) late neonatal death (n=2)	1 2 3 4 5 6

***Data sources:** 1 = ANC pregnancy cards; 2= Face-to-face interview; 3= Labour follow-up sheets, delivery summaries and maternal medical records; 4= Newborn's clinical records, 5= Newborn´s clinical observation by the PhD researcher and 6= mobile phone call follow-up after the 28th day of the newborn life.

Research and field work photographs can be consulted in Appendix 12.

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Adolescent pregnancy in Sao Tome and Principe: a cross-sectional hospital-based study

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Abstract

Background: Pregnancy starts early in Sao Tome and Principe (STP) and rates of adolescent pregnancy increased 16% in recent years reaching a 27.3% prevalence. This study aimed to understand the pregnant adolescents' characteristics and factors associated to early childbearing in STP.

Methods: A cross-sectional hospital-based study was undertaken in Hospital Dr. Ayres de Menezes between 2016 and 2018 with a randomly selected total sample size of 518 mothers. Mothers' clinical records and interviews were used to collect relevant data. The results among adolescent girls 19 years of age and younger (n=104) were compared to adult mothers (n=414). A subgroup analysis of adolescent pregnant girls was also conducted. Statistically significance was considered at a p-value ≤0.05. Data were analysed using SPSS software.

Results: The study revealed that 20.1% were adolescent mothers. Pregnancy at a very early age (≤15) was experienced by 7.7%. The characteristics founded to be positively associated with adolescent pregnancy were: 1) being single (OR 0.39, 95% CI=0.2–0.6, p≤0.001); 2) having a relationship with the baby´s father for a period of less than one year (OR 0.16, 95% CI=0.09-0.3, p≤0.001); 3) lack of the baby´s father support (OR 0.41, 95% CI=0.2–0.7, p=0.002); 4) not using a contraceptive method (OR 0.33, 95% CI=0.2–0.5, p≤0.001), and 5) inappropriate knowledge concerning the identification of the newborn's danger signs (OR 15.7, 95% CI= 9–26, p≤0.001). Comparing pregnancy at very early age (≤15) to late (>18 and ≤19) adolescents, main differences were that previous contraceptives were not used at all in girls ≤15 years compared to 9.8% of late childbearing subgroup.

Conclusions: Unfavourable factors linked to adolescent pregnancies were absence of a contraceptive method, getting pregnant in the early first months of one relationship and to be single. Gap age difference between adolescents' partners, polygamous sexual relationships, previous abortion and having already other living children were also identified. Adolescents also had inappropriate knowledge of the identification of the newborns' danger signs. Before being sexually active, adolescents critically need sexual and reproductive health information provided by a healthy community and through school programmes on sexual education. Schools should promote girl's empowerment and awareness and, at the same time, reinforce boy's role in fatherhood and shared responsibilities. The government should work on the prevention of early sexual initiation, as well as on improving family planning programmes to protect

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them from pregnancy with special focus for the very early adolescent girls. None of these goals can be achieved if the government doesn't, simultaneously, improve educational and economic opportunities for girls.

Keywords: Adolescent pregnancy, Sao Tome and Principe, Family planning, Newborns' danger signs

Background

Adolescence is a critical phase for a successful transition to adulthood, that is threatened by becoming pregnant under 19 years old as it can greatly alter young women´s life prospects and those of their children [1, 2]. Adolescent pregnancies are a global problem as babies born to adolescent girls account for 11% of all births, with 95% occurring in developing countries [3]. Worldwide, adolescent pregnancies are frequently unplanned, unwanted, and out of wedlock that blocks girls' education and their social relationships due to stigmatisation and loss of self-esteem, compromising the adolescents' economic independence [1, 3–7]. Consequently, early motherhood impacts not only girls' mental and physical health, but it also promotes an intergenerational perpetuation of a poverty trap and cycle [1, 2]. Thus, helping adolescent girls to avoid facing childbearing can have far-reaching benefits for them, their children, and societies [1, 3–7].

Recognizing the adolescents' vulnerabilities is the first step in approaching this problem. In Africa, according to Kassa et al. 2018 meta-analysis [8], girls were more likely to start childbearing if they were from rural residence, married, not educated, whose parents had no education, and from families that lack parent to child communication on sexual reproductive health issues. Similar findings were also published by Ahinkorah et al. 2021 multi-country analysis [9], except for the finding that girls who lived in rural areas had lower odds of first adolescent pregnancy [9].

Delaying childbearing requires focusing on its major underlying factors: timing of first sex and ineffective contraceptive use, usually associated to girls' inadequate sexual knowledge; low risk perceptions; ambivalence towards sex; lack of power to negotiate safer sex options and to deal with older partner´s persuasive techniques towards sex [10–13]. Moreover, adolescent girls face a higher risk for unsafe abortion and to be a second time young mothers [10, 14, 15]. Pregnancies complications are more frequent, and babies of adolescent mothers are at a higher risk of being born premature, dying in the neonatal period [16] and facing malnutrition, low mental and physical development, inappropriate social connection with parents and poor education [11, 17, 18]. In general, these risks are lower for adolescents in their late teens but those who give birth before age 15 are at much higher risk [10, 19]. Additionally, the younger the girl the less likely is for her to attend antenatal healthcare as coverage among younger adolescents are lower when compared to older adolescents (18-19 years old) [20] (https://data.unicef.org/topic/child-health/adolescent-health/).

In Africa, this problem is even more hazardous as 33% of girls are giving birth before the age of 18 and 3.5% even before the age of 15 years old [3, 21–23].

Furthermore, it is foreseen that the percentage of adolescent pregnancies will increase globally by 2030, particularly in the Sub-Saharan African countries [22]. These can be due to girls' low economic status, poor living arrangements, early school drop-out, inappropriate knowledge of sexual and reproductive health issues, absence of family planning, lack of sexuality education in schools and low employment attainment [8].

This calls for efforts to address the sexual and reproductive health problems of adolescent girls, included for the first time in the Sustainable Development Goals (SDGs) Countdown to 2030 [24, 25]. First step should start in the empowerment of girls attending school, preventing their drop-out and giving them access to sexual education with the necessary skills to prevent pregnancy [8].

The Democratic Republic of Sao Tome and Principe (STP), two islands in the Gulf of Guinea, has one of the highest rates of teenage pregnancies in sub-Saharan Africa, estimated at about 27% [26, 27]. Pregnancy starts early in STP and adolescent pregnancy rate in the past years increased by 16% (22.8% in 2009 to 27.3% in 2014). With a population of about 200.000, STP has a high adolescent fertility rate of 94.8 births per 1,000 women aged 15 to 19 years compared for example to 68 in South Africa or 61 in Sudan [23, 27–30]. Although, adolescent pregnancy is recognized as a major public health issue in the country and the government seeks to be able to reduce it to a rate of 15% [28, 31–36] (https://www.un.org/en/development/desa/population/publications/pdf/popfacts/PopFacts_2019-1.pdf), it has not been yet properly studied [21, 31–33, 37].

This study therefore sought to investigate the differences between adolescents and older women in relation to selected sociodemographic and family characteristics, obstetric history, and knowledge of the identification of the newborns' danger signs. We also aimed to explore the eventual differences of "very early childbearing" defined as birth before age ≤15, early childbearing (birth between age >16 and ≤17) and late

childbearing (birth age >18 and ≤19) in comparison to the older women group trying to figure out main teen's vulnerabilities.

We have previously studied these adolescent girls regarding their adverse outcomes and founded that foetal distress and the need for performance of neonatal resuscitation manoeuvres were the main adverse perinatal outcomes imputable to these adolescent births.

We believe that understanding the characteristics of pregnant adolescents and risk factors that promote early childbearing will support STP policy makers in order to design pragmatic interventional programs to reduce the countries overwhelming high rates of adolescent pregnancies and achieving key SDG [34].

Material and methods

Study design

This is a cross-sectional analytical hospital-based study conducted between July 2016 to November 2018.

Study context

The study was located at Hospital Dr. Ayres de Menezes (HAM) in Sao Tome city, the capital of STP, a rapidly growing city, with 64% of the population living in the capital [33]. HAM is the only hospital in the island, with a maternity that delivers around 4700 babies annually, around 82,4% of all the deliveries in the country [32]. Comprehensive Emergency Obstetric and Neonatal Care Services are available at HAM. There are 6 health centres with maternities in the rural area.

Study population and sampling

Mothers were randomly selected by chance and the study was done in different months to avoid seasonal interference and effects by means of confounding variables by guaranteeing a sample with few biases. Two groups were considered, over or under and equal to 19 years of age. Of the total 518 pregnancies, 104 were in women aged ≤19 years (adolescent group) and 414 pregnancies in women more than 19 years of age (older childbearer group). For some variables (Tables 1, 2 and 4) further analyses with three adolescents age subgroups were used for the purpose of finding eventual differences of "very early childbearing" as birth before age ≤15 (n= 8), early childbearing for birth between age >16 and ≤17 (n=45) and late childbearing for birth age >18 and ≤19 (n=51) in comparison to the older women group.

Eligibility criteria

All women admitted to the hospital for delivery with a gestational age of 24 weeks or more were eligible to be enrolled in the study. Those who gave birth outside the hospital but were admitted for postnatal were also included in the study.

Data collection

A face-to-face interview by the main investigator was conducted with the mothers before discharge to gather information regarding socio-demographic characteristics, antenatal care/obstetric history, and their knowledge of identification of newborns' danger signs (signs and symptoms of disease). The survey was built in the tool QuickTapSurvey© and mothers' answers were collected and entered to this app. Data regarding obstetric and antenatal care were also checked and collected from medical records and antenatal care pregnancy booklet into the app survey.

Variables included in the study

Sociodemographic characteristics included: (i) residence, (ii) standard of living, (iii) marital status, (iv) living arrangements, (v) mother's education level, (vi) mother's employment status, (vii) baby´s father age, (viii) father´s education level, (ix) father´s employment status and (x) father´s living with other woman/houses according to pregnant women´s answer during the interview.

Residence was grouped into urban and rural, urban residence considered for women living at the capital city (Água Grande) and rural in all other districts.

Standard of living was categorized according to household deprived or not of electricity, sanitation, drinking water, cooking fuel and type of housing as Sustainable Development Goal guidelines [38].

Marital status considered the two categories yes (married/union) or no if single/never married. Time of the union/marriage was also assessed.

Mother's and father's education level was categorized as either elementary only or secondary level. Taking into consideration that not attending secondary school, usually beginning from the age of 12 years old, is considered to have an inappropriate educational level.

Employment status were collected and classified as no if "not employed" or yes if "employed" (lists of jobs were merged) regardless of the type of job.

Obstetric and antenatal characteristics included: (i) obstetric history, (ii) unplanned pregnancy, (iii) previous contraceptive use, (iv) family planning after current pregnancy, (v) antenatal care visits.

Antenatal care (ANC) consisting of less than 4 of expected consultations during pregnancy was considered as inadequate, between 4-7 as adequate and 8 or more visits as complete.

Gravidity categorized as primigravida (1), multigravida (2-4) and grandmultigravida (5 or above).

Table 1 Socio-demographic characteristics for different adolescent subgroups and total adolescent pregnant girls in comparison to the older women group

Characteristics	Pregnancies ≤19 years old				Pregnancies >20 years old
	very early childbearing (≤15) *n*= 8 (%)	early childbearing (≥16 and ≤17) *n*=45 (%)	late childbearing (≥18 and ≤19) *n*=51 (%)	Total adolescents *n*= 104 (%)	*n*=414 (%)
Residence					
rural	6 (75%)	30 (67%)	27 (52.9%)	63 (60.6%)	213 (51.4%)
urban	1 (12.5%)	15 (33%)	22 (43.2%)	38 (36.5%)	194 (46.9%)
missings	1 (12.5%)	-	2 (3.9%)	3 (2.9%)	7 (1.7%)
OR and 95% CI	0.1 (0.02-1.5)	0.5 (0.29-1.06)	0.8 (0.48-1.59)	0.66 (0.4-1.03)	
p value	0.11	0.07	0.66	0.07	
Mother´s education level					
elementary only	5 (62.5%)	20 (44%)	19 (37.3%)	44 (42.3%)	160 (38.6%)
secondary	3 (37.5%)	25 (56%)	32 (62.7%)	60 (57.9%)	254 (61.4%)
OR and 95% CI	2.8 (0.66-11.9)	1.4 (0.75-2.63)	0.9 (0.5-1.8)	1.3 (0.9-2)	
p value	0.16	0.29	0.99	0.19	
Employed					
no	5 (62.5%)	31 (69%)	32 (64%)	68 (65.4%)	262 (63.3%)
yes	-	1 (2%)	7 (14%)	8 (7.7%)	134 (32.4%)
missings	-	-	1 (6.3%)	1 (0.9%)	9 (2.2%)
OR and 95% CI	-	-	-	0.17 (0.8-0.37)	
p value	-	-	-	≤0.001*	
Still studying					
yes	3 (37.5%)	13 (29%)	11 (22%)	27 (26%)	9 (2.2%)
OR and 95% CI	-	-	-	15.8 (7-35)	
p value	-	-	-	≤0.001**	
Married					
no	6 (75%)	14 (31%)	13 (25.5%)	33 (31.7%)	59 (14.3%)
yes	2 (25%)	31 (69%)	37 (72.5%)	70 (67.3%)	336 (81.2%)
missings	-	-	1 (2%)	1 (1%)	19 (4.6%)
OR and 95% CI	0.05 (0.01-0.2)	0.34 (0.16-0.7)	0.46 (0.23-0.9)	0.39 (0.2-0.6)	
p value	≤0.001	0.003	0.03	≤0.001***	
Babies' father support					
yes	6 (75%)	34 (76%)	44 (86.3%)	84 (80.7%)	373 (90.1%)
no	2 (25%)	11 (24%)	7 (13.7%)	20 (19.2%)	41 (9.9%)
OR and 95% CI	0.3 (0.06-1.7)	0.34 (0.1-0.7)	0.7 (0.29-1.6)	0.41 (0.2-0.7)	
p value	0.19	0.005	0.42	0.002****	
Father´s age					
<20 years old	2 (25%)	11 (24%)	4 (9.1%)	17 (16.3%)	2 (0.5%)
20-29	5 (62.5%)	27 (60%)	33 (75%)	65 (62.5%)	124 (30%)
30-39	-	3 (7%)	7 (15.9%)	10 (9.6%)	161 (38.9%)
40-49	-	-	-	-	64 (15.5%)
>49	-	-	-	-	25 (6%)
missing	1 (9.2%)	4 (9%)	7 (13.7%)	12 (11.5%)	38 (9.2%)
OR and 95% CI	-	-	-	-	
p value	-	-	-	-	
Father´s education level					
elementary only	3 (37.5%)	9 (20%)	16 (31.4%)	28 (26.9%)	129 (31.2%)
secondary	3 (37.5%)	15 (33%)	19 (37.2%)	37 (35.6%)	151 (36.5%)

Table 1 (continued)

Characteristics	Pregnancies ≤19 years old				Pregnancies >20 years old
	very early childbearing (≤15) *n*= 8 (%)	early childbearing (≥16 and ≤17) *n*=45 (%)	late childbearing (≥18 and ≤19) *n*=51 (%)	Total adolescents *n*= 104 (%)	*n*=414 (%)
doesn´t know/missing[†]	2 (25%)	21 (47%)	16 (31.4%)	39 (37.5%)	134 (32.4%)
OR and 95% CI	-	-	-	-	
p value	-	-	-	-	

Abbreviations: *OR* Odds Ratio, *CI* Confidence interval

*The adolescent group reported to have a job in 7.7% compared to a higher proportion of 32.4% for the older counterpart with a significant statistical difference (OR 0.17, 95% CI=0.8-0.37, $p \leq 0.001$).

**There was a higher proportion of adolescent mothers who were students at the time they got pregnant, with a statistically significant difference (OR 15.8, 95% CI=7-35, $p \leq 0.001$).

***67.3% of the teenage girls were married and 31.7% were single compared to 81.2% and 14.3% in the older women group, which was statistically significant (OR 0.39, 95% CI=0.2-0.6, $p \leq 0.001$).

****The adolescent´s pregnancy was not supported/followed by the baby´s father in 20% of the cases compared to 9.9% of the older women group, the difference being statistically significant (OR=0.41, 95% CI=0.2–0.7, $p=0.002$).

[†]Most adolescents didn´t answer because they were not aware of the fathers' education level achieved

In each survey, women were asked about previous contraception use and about their future desire to have a contraception method after the pregnancy including the type of contraceptive method they wish to use. We considered as traditional contraceptives the following methods: rhythm, calendar, withdrawal, lactation amenorrhea and "other traditional" methods. As modern contraceptives, we included intrauterine devices and systems, subdermal implants, oral contraceptives, injectable, diaphragms and cervical caps, condoms (male and female), patch, emergency contraception and sterilization.

Mother´s knowledge of identification of newborns' danger signs: was assessed during the interview as "yes" or "no" answer grouped and organized according to the definition presented by the WHO and the Young Infants Clinical Signs study group [39, 40] to the following questions: "Do you think the following are danger signs in the newborn?" (i) convulsions/spasms/rigidity; (ii) difficult/fast breathing; (iii) very small baby (less than 2.5 kg) or losing weight in the first weeks of life; (iv) lethargy/unconsciousness; (v) fever; that is high body temperature that makes the newborn body hot. A score of 3 or more "yes"answers was considered as appropriate knowledge and less than 2 "yes" answers as inappropriate. Locally appropriate and known terms in the appropriate cultural area were used for clinical simplicity purpose and mother´s understanding.

Data management and statistical analysis

The data were secured in a confidential and private location. Participants were referred to by identification numbers and the informed consent forms were kept separate from the questionnaires. Both could only be linked by a coding sheet available only to the investigators. The software used for sample calculation was Raosoft (http://www.raosoft.com/samplesize.html), but this value was supported by pass software (https://www.ncss.com/software/pass/). There was a mean of 4540 HAM deliveries/year within the study period. The sample was calculated based on a minimum sample of 10% of the population validated by the sample calculation software, which placed the right dimension between 355 (95%) and 579 (99%) confidence. It was possible to collect 518, which gave some comfort at this level. Differences in the demographic and obstetric characteristics between the adolescent and adult mother were assessed using the Pearson's chi-squared test ($\chi 2$). During data analysis, missing values were treated as missing.

The associations between maternal age were categorized as adolescent mothers (1) vs others (0). For each outcome with a statistically significant difference at the first level, further analysis was developed using mothers´ age as a continuous variable with adjustments made simultaneously for father´s support and contraceptive use independently of their statistical significance. For statistical purpose, maternal age was kept as a continuous variable in the models. Mean age of the mothers was 26.59 years (sd 7.1), with a quasi-normal distribution, just underrepresented at the very young mother's level. Two step logistic regression models were developed to assess the power of age as a predictor. The models were adjusted for marital status, education and antenatal care, the probabilities of event were recorded for each case and the plots obtained with the respective 95% CI for

Table 2 Obstetric history, ANC and family planning for the different adolescent subgroups in comparison to the older women group

Characteristics	Pregnancies ≤19 years old				Pregnancies >20 years old
	very early childbearing (≤15) *n*= 8 (%)	early childbearing (≥16 and ≤17) *n*=45 (%)	late childbearing (≥18 and ≤19) *n*=51 (%)	Total adolescents *n*= 104 (%)	*n*=414 (%)
Previous contraceptive use					
yes	0 (0%)	2 (4%)	5 (9.8%)	7 (6.7%)	119 (28.7%)
no	7 (87.5%)	36 (80%)	41 (80.3%)	84 (80.7%)	217 (52.4%)
missings[#]	1 (12.5%)	7 (16%)	5 (9.8%)	13 (12.6%)	78 (18.8%)
OR and 95% CI	-	0.14 (0.03-0.59)	0.24 (0.08-0.6)	0.33 (0.2-0.5)	
p value	-	0.007	0.007	≤0.001*	
Pregnancy was planned					
yes	0 (0%)	5 (11%)	14 (27.4%)	19 (18.3%)	102 (24.6%)
no	5 (62.5%)	30 (67%)	25 (49%)	60 (57.7%)	231 (55.8%)
missings[#]	3 (37.5%)	10 (22%)	12 (23.5%)	25 (24%)	81 (19.6%)
OR and 95% CI	-	0.39 (0.1-1.0)	1.2 (0.6-2.5)	-	
p value	-	0.06	0.49	-	
Gravidity					
1	7 (87.5%)	39 (87%)	27 (52.9%)	73 (70.2%)	54 (13%)
2	1 (12.5%)	5 (11%)	19 (37.3%)	25 (24%)	78 (18.8%)
3 or more	0 (0%)	1 (2%)	5 (9.8%)	6 (5.8%)	282 (68.1%)
OR and 95% CI				17.7 (9-26)	
p value				≤0.001**	
Abortion/ miscarriage					
0	7 (87.5%)	41 (91%)	41 (82%)	89 (85.5%)	274 (66.2%)
1	1 (12.5%)	4 (9%)	9 (18%)	14 (13.5%)	105 (25.4%)
2	0 (0%)	0 (0%)	0 (0%)	0	22 (5.3%)
>3	0 (0%)	0 (0%)	0 (0%)	0	13 (3.1%)
OR and 95% CI				-	
p value				-	
Living children					
0	8 (100%)	43 (96%)	35 (68.6%)	86 (82.7%)	74 (17.9%)
1	0 (0%)	2 (4%)	13 (25.5%)	15 (14.4%)	89 (21.5%)
2	0 (0%)	0 (0%)	3 (5.9%)	3 (2.9%)	97 (23.4%)
>3	0 (0%)	0 (0%)	0 (0%)	0	154 (37.2%)
OR and 95% CI				-	
p value				-	
1st attendance ANC					
<12th	3 (37.5%)	18 (40%)	34 (66.6%)	55 (52.9%)	218 (52.7%)
>12th	3 (37.5%)	22 (49%)	12	37 (35.6%)	136 (32.8%)
missings	2 (25%)	5 (11%)	5 (9.8%)	12 (11.5%)	60 (14.5%)
OR and 95% CI	0.8 (0.17-4.3)	0.7 (0.3-1.4)	2.47 (1.2-4.9)	-	
p value	0.87	0.39	0.01	-	
ANC					
at least once				104 (100%)	413 (99.7%)
<4 visits	2 (25%)	8 (18%)	5 (9.8%)	15 (14.4%)	55 (13.3%)
4-7 visits	4 (50%)	21 (47%)	20 (39.2%)	45 (43.3%)	196 (47.3%)
>8 visits	2 (25%)	16 (36%)	26 (51%)	44 (42.3%)	163 (39.4%)
OR and 95% CI				-	
p value				-	

Table 2 (continued)

Characteristics	Pregnancies ≤19 years old				Pregnancies >20 years old
	very early childbearing (≤15) *n*= 8 (%)	early childbearing (≥16 and ≤17) *n*=45 (%)	late childbearing (≥18 and ≤19) *n*=51 (%)	Total adolescents *n*= 104 (%)	*n*=414 (%)
Want to do family planning					
yes	1 (12.5%)	34 (76%)	16 (31.3%)	51 (49%)	165 (39.9%)
no	0 (0%)	1 (2%)	3 (5.9%)	4 (3.8%)	39 (9.4%)
missings[#]	7 (87.5%)	10 (22%)	32 (62.8%)	49 (47.1%)	194 (46.9%)
OR and 95% CI				0.66 (0.4-1.03)	
p value				0.07	

as don't know, doesn't want to reply

Abbreviations: *ANC* Antenatal care, *OR* Odds Ratio, *CI* Confidence interval.

* Previous contraceptive use was stated in 6.7% of the teenage group and in 28.7% of the older counterpart, what is a significant statistically difference (OR =0.33, 95% CI = 0.2–0.5, $p \leq 0.001$).

** The proportion of primigravidas among teenagers in relation to those aged >20 years was statistically significant (OR 15.7, 95% CI= 9-26, $p \leq 0.001$).

each age point. Regarding confounding variables, multivariate logistic regressions were performed in two stages - first only with the variable under study (mother's age) and afterwards with the inclusion of control variables to understand whether the identified effect occurred via others (education, partner and antenatal care).

Statistical significance was defined as $p<0.05$.

Data were entered in QuickTapSurvey (©2010-2021 Formstack), and the dataset exported to Excel for cleaning and further analysis using the Statistical Package for the Social Sciences for Windows, version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Ethics approval and consent to participate

Ethical clearance was obtained from the Democratic Republic of Sao Tome and Principe Ministry of Health and Hospital Dr. Ayres de Menezes. Written informed consent was obtained from all participants (or their parent or legal guardian in the case of teenage under 16) after the purpose of the research was explained orally by the investigator. This was done only after delivery to reduce coercion due to labour pains. Participation in the survey was voluntary, as participants could decline to participate at any time during the study. All methods were performed in accordance with the relevant guidelines and regulations in practice.

Results

Socio-demographic and family characteristics

A total of 518 pregnant women were enrolled. Among the enrolled women, 20.1% (CI – 16,3% to 23%) were adolescents, with 104 teenage pregnancies (≤19 years old) and 414 deliveries in older women. The mean age was 17.42, median 17, with a minimum age 14 years. Regarding childbearing subgroup ages (Fig. 1), 7.7% (8) were very early childbearing adolescents (birth age ≤15), 43.3% (45) were early (≥16 and ≤17) and 49% (51) were late (≥18 and ≤19).

The older women group mean age was 28.9 years, median of 28 with a maximum age of 43 years. Regarding the adult group, the mother´s mean age at first pregnancy was 20.1 (±3.76 SD) years (minimum 13, maximum 36).

Socio-demographic characteristics for the different adolescent subgroups in comparison to the older women group are described in Table 1.

Marriage, living arrangements and baby´s father support

The duration of the relationship/union or marriage was shorter for the younger ages: 59.5% (62/104) of those were in the union less than one year compared to 19.7% (81/414) of the older counterpart, this was statistically significant (OR 0.16, 95% CI 0.09-0.3, $p \leq 0.001$). In terms of existence and acknowledgment of a "polygamous" marital informality, 11.6% (12/104) of the adolescent girls reported they knew that the baby´s father was also living with another woman compared to 20.6% (85/414) in the older group, although it should be noticed that 48.5% (50/104) of the adolescent girls and 36.1% (149/414) of the older women group preferred not to answer to this question.

Concerning living arrangements, 68% (71/104) of the adolescents were living with their husbands/boyfriend and 28.7% with others: 13.4% (14/104) with the pregnant woman´s mother and 15.3% (16/104) with other relatives;

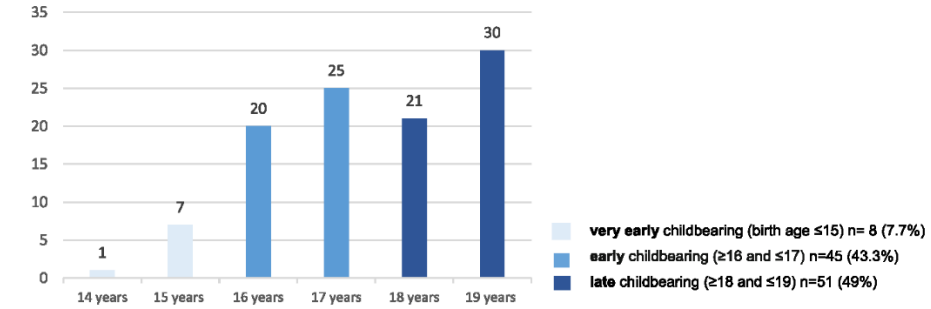


Fig. 1 Adolescent ages and childbearing subgroup ages

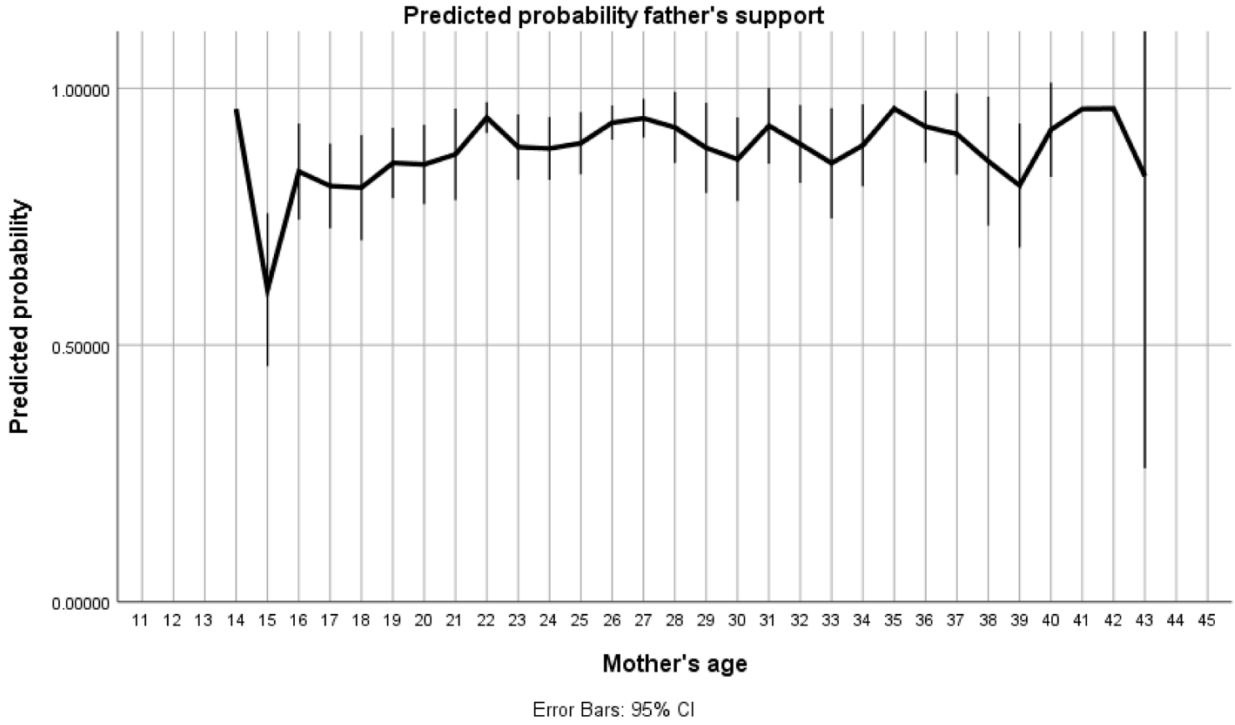


Fig. 2 Father´s support according to mother´s age. The line at 0.5 represents equal probability of father's support during pregnancy

1.9% (2/104) adolescents mentioned that they were living alone. Three hundred and fifty-three/414 (85%) of the older women were living with their husbands/men, 4.5% (19/414) alone, 4.5% (19/414) with the pregnant woman´s mother, 4.1% (17/414) with other relatives and 2.2% (9/414) were living with a man who was not the baby´s father.

The adolescent´s pregnancy was not supported/followed by the baby´s father (Table 1) in 20% of the cases with a statistically significant difference (OR 0.41, 95% CI 0.2–0.7, p=0.002) comparing to the older counterpart. However, after the model was adjusted for marital status, education and antenatal care, the effect of age disappeared totally, as the relevant variable becomes marital status (Fig. 2). In the controlled model, marital status showed a OR 19, with a p=0.001.

Obstetric history and antenatal care

Gravidity, abortions, and number of living children are described in Table 2.

Previous contraceptive use and future family planning

Previous contraceptive use is described in Tables 2 and 3.

Table 3 Future family planning: methods women are willing to use to prevent future pregnancy

	Adolescent group *n*=51 (%)	Older counterpart *n*= 165 (%)
Oral contraceptives	8 (15.6%)	43 (26%)
Injectables	6 (11.7%)	44 (26.7%)
Intra uterine device	3 (5.8)	8 (4.8%)
Sterilization	0	23 (14%)
Condom (male)	0	0
Traditional methods*	34 (66.7%)	32 (19.4%)
OR and 95% CI	0.66 (0.4-1.03)	
p value	0.07	

* Rhythm, Calendar, Withdrawal, Lactation amenorrhea

referred they would choose the use of a condom by their partner. To note that two older women had an urgent hysterectomy at the time of the current birth and other 7.9% (13/165) performed a sterilization during the caesarean intervention.

Mothers´ knowledge of identification of newborns' danger signs

Mothers´ knowledge of identification of newborns' danger signs was inappropriate in 70.2% (73/104) of the adolescent group and in 13% (54/414) of the older childbearers, being statistically significant (OR 15.7, 95% CI 9–26, $p \leq 0.001$).

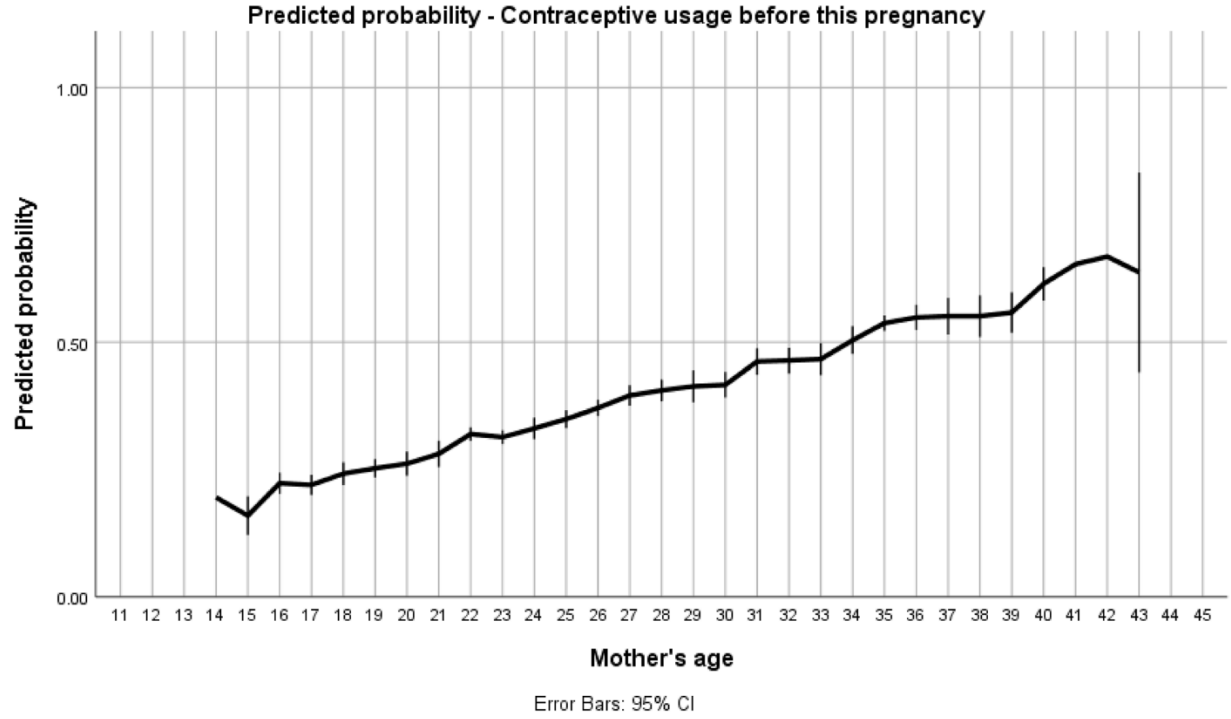


Fig. 3 Previous contraceptive use according to women´s age. The model was adjusted for marital status, education, and antenatal care. The line at 0.5 represents equal probability of contraception before birth

When model was adjusted for marital status, education, and antenatal care, the probability of using contraception rises with age, with a turning point at 34 years old (Figure 3), meaning that in Sao Tome and Principe most young women do not assume birth control (Table 2).

Methods women stated that are willing to use to prevent future pregnancy are described in Table 3. Adolescent group most rated (66.7%) preference were for traditional methods (rhythm, calendar, withdrawal, lactation amenorrhea). In this study none of the group

Very early, early, and late childbearing adolescents in comparison to older pregnant women

For some variables (Tables 1, 2 and 4) age subgroups were used for the purpose of analysing eventual differences between "very early childbearing" for birth before age ≤15 (n= 8), early childbearing for birth between age >16 and ≤17 (n=45) and late childbearing for birth age >18 and ≤19 (n=51).

Regarding standard of living (Table 4) almost all women in the study were considered as having a deprived

Table 4 Standard of living for the different adolescent subgroups in comparison to the older women group

Characteristics	Pregnancies ≤19				Pregnancies >20
	very early childbearing (≤15) *n*= 8 (%)	early childbearing (≥16 and ≤17) *n*=45 (%)	late childbearing (≥18 and ≤19) *n*=51 (%)	Total adolescents *n*= 104 (%)	*n*=414 (%)
Electricity					
No	2 (25%)	12 (27%)	9 (17.6%)	23 (22%)	86 (20.8%)
Yes	6 (75%)	33 (73%)	42 (82.4%)	81 (78%)	317 (76.6%)
missings	-	-	-	-	11 (2.7%)
OR and 95% CI	0.17 (0.08-0.2)	0.69 (0.3-1.4)	1.3 (0.6-2.9)		
p value	0.87	0.29	0.43		
Sanitation					
open defecation	6 (75%)	31 (69%)	24 (48%)	61 (58.6%)	182 (44%)
latrine	2 (25%)	9 (20%)	24 (48%)	35 (33.6%)	122 (29.5%)
toilet	-	4 (9%)	2 (4%)	6 (5.8%)	94 (22.7%)
missings	-	1 (2%)	1 (2%)	2 (1.9%)	16 (3.9%)
OR and 95% CI	0.32 (0.08-1.22)	0.5 (0.31-0.22)	0.7 (0.4-1.0)		
p value	0.09	0.06	0.07		
Drinking water					
river	-	4 (9%)	5 (10.4%)	9 (8.6%)	37 (8.9%)
public tap	4 (50%)	8 (18%)	12 (25%)	24 (23%)	109 (26.3%)
protected well	4 (50%)	15 (33%)	12 (25%)	31 (29.9%)	63 (15.2%)
piped water outdoor	-	15 (33%)	16 (33.3%)	31 (29.9%)	152 (36.7%)
piped water indoor	-	3 (7%)	3 (6.3%)	6 (5.7%)	46 (11.1%)
missings	-	-	3 (6.3%)	3 (2.9%)	7 (1.7%)
OR and 95% CI					
p value					
Cooking fuel					
wood	1 (12.5%)	18 (40%)	16 (31.4%)	35 (33.6%)	127 (30.7%)
charcoal/coal	5 (62.5%)	22 (49%)	31 (60.8%)	58 (55.8%)	235 (56.8%)
gas	2 (25%)	5 (11%)	4 (7.8%)	11 (10.6%)	41 (9.9%)
missing	-	-	-	-	11 (2.7%)
OR and 95% CI	-	0.8 (0.5-1.1)	1.0 (0.6-1.6)		
p value	-	0.55	0.98		
Housing					
wood	8 (100%)	41 (91%)	46 (90.2%)	95 (91.3%)	328 (79.2%)
mixt	-	3 (7%)	1 (2%)	4 (3.8%)	44 (10.6%)
brick house	-	1 (2%)	4 (7.8%)	5 (4.8%)	31 (7.5%)
missing	-	-	-	-	11 (2.7%)
OR and 95% CI	-	0.5 (0.2-1.2)	0.7 (0.43-1.2)		
p value	-	0.13	0.38		

Abbreviations: *OR* Odds Ratio, *CI* Confidence interval

standard of living (no electricity and/or open defecation and/or river, and/or cooking wood and coal and/or housing wood or mixt).

A non-statistically significant trend was observed among teenage mothers living in rural areas compared to their older counterpart.

Child marriage was reported in 25% (2/8) of the very early childbearing adolescents and in 69% (31/45) in the early childbearing (birth age >16 and ≤17). When comparing marital status, a statistically significant difference (OR 0.05, 95% CI 0.011-0.276, p=0.0001) was found between very early childbearing; (OR 0.35, 95%

CI 0.17-0.7, p=0.003) early childbearing and (OR 0.464, 95% CI 0.23-0.93, p=0.03) late childbearing and older women (Table 1).

With respect to the use of previous contraceptives, these were not used at all in girls ≤15 years, when comparing to 9.8% (5/51) of late childbearing (birth age >18 and ≤19) (Fig. 3 and Table 2).

A total of 14 teenage girls had already experienced a previous abortion: 12.5% (1/8) for very early childbearing; 9% (4/45) in early childbearing subgroup and 18% (9/51) in the late childbearing adolescent. To highlight that 4% of girls between 16 to 17 years old had already one living child. The late childbearing group had already one living child in 25.5% and 5.9% had already two other living children and were expecting the third son before completing her 20th birthday (Table 2).

Regarding differences in the first attendance at ANC facility there was a statistically significant difference between the late childbearing subgroup compared to the older counterpart in attending before the 12th week of pregnancy (OR 2.47, 95% CI 1.24-4.95, p=0.01) (Table 2).

Discussion

Early motherhood is a major public health issue in Sao Tome and Principe that impacts not only girls' health and future, but also maintains an intergenerational poverty cycle in the country [1, 2]. This study aimed to recognize pregnant adolescent main vulnerabilities to support policy makers in delineating a strategy for preventing the high rates of adolescent pregnancies in the country.

In this study, we found an adolescent pregnancy prevalence of 20.1%, lower compared to the rate of 27% published for the country [26, 27]. This difference can be related to the type of study design of a hospital-based contrarily to a demographic health survey.

A rate of 7.7% of very early adolescent child bearers (14 and 15 years) was identified, a rate two-times higher than the 3.5% published in Africa [3, 21–23] (https://data.unicef.org/topic/child-health/adolescent-health/). Although very early adolescent childbearing is generally rare [41], three of the four countries in the world with more than 10 births per 1,000 girls under 15 years are in sub-Saharan Africa, namely Angola, Mozambique, and Nigeria (https://www.un.org/en/development/desa/population/publications/pdf/popfacts/PopFacts_2019-1.pdf). Our findings suggest that pregnancy under 15 years old is not so rare in Sao Tome and Principe and focus should be given to these biological, social, economic, and emotional particularly more vulnerable girls. In STP, the minimum age at which an individual is considered legally old enough to consent to participation in sexual activity is 14 years old and we didn't find any girl under this age.

Adolescent girls were particularly more vulnerable concerning to their bond and type of relationship established with the baby´s father due to the reasons next discussed.

First, we found that a high proportion of teenage pregnancies occurred in the first months of the beginning of the union/relationship compared to the older women group (p≤0.001), revealing girls' immaturity and lack of awareness and skills to prevent pregnancy, especially when most adolescent girls stated that the pregnancy was not planned.

Second, previous contraceptive methods were not used at all in girls younger than 15 years old and in most of girls aged between 16 and 19 years. These findings are similar to most studies in Sub-Saharan Africa that report that few sexually active adolescents use contraceptives methods [42–44]. As described in another study, 51% (26/51) of the pregnant adolescent in STP did not use any contraceptive method, mainly because their partners refuse to do so, and the preferred contraceptive method were condoms (41.2%) [31]. Contrarily, to notice that the use of condoms was not an option among the participants of our study.

Third, regarding age-disparate sexual relationships, a big age-gap between sexual partners was found. This age difference, which could be of fifteen years, when referring to very young girls and their partners would be considered sexual abuse in many societies. These relations between women and men translate that women often have less power than their partners in relationships, especially if they are much younger than them [10–13]. One implication of these findings is that pregnant adolescents with older partners are, therefore, a particularly at-risk group and should be prioritized for targeted delivery of sexual reproductive health services. As known, women's self-efficacy in negotiating condom or other contraceptive use, their capability of sexual communication with their male sex partners and their perceptions of whether their male sex partners were currently having sex with other women is biased and unbalanced, particularly with adolescents and when there is a big age difference between partners [10, 11, 45].

Regarding union or marriage, we found differences between the teenage subgroups, if the 14-15 years old adolescents were mainly single, those aged between 16 and 19 years old were married. These results showed a significant statistical association regarding the status "single" between adolescents and older women group. On the other hand, child marriage, defined as marriage occurring before the age of 18, was founded in a high rate for the early childbearing girls (16-17 years). This reality is well-known in the country with 15.3% of the girls aged 15-19 years to be legally married or in a union; 5.1% before the age of 15 and 32.2% before the age of 18

years [33]. Family Law in the country enables parents to authorize the marriage of children under 18, provided that the woman has already completed 14 years of age and the man has completed 16 years of age [46], what can also promote adolescent pregnancies in the country.

Concerning baby´s father support we initially found a statistically significant difference between groups (p=0.002), with the adolescent group in disadvantage. However, taking into consideration the very high prevalence of single parent families in the country [28], the model was adjusted, and the effect of age disappeared totally for father´s support. Other characteristic notable of discussion is that both adolescents and older women acknowledged that the baby´s father was also living with another woman, which is probably associated with a "polygamous" marital informality that is known in the country to be around 22.4% [28]. This can be explained by the fact that in STP, many families live in a kind of non-marital union, which consists of regular or irregular visits by the male spouse to the women with whom he has sexual relations, usually a young woman, with children resulting from this relationship [35, 36].

These culture characteristics can have a particular effect on family planning choices, mainly in contraceptive use and planned pregnancy. For instance, this study demonstrates that unplanned pregnancies are a problem in the country to most women regardless their age and that the probability of using contraception rises with age, with a turning point at 34 years old.

In contrast, some girls reported that they had planned to fall pregnant. The reason why they have planned to be pregnant at such a younger age was not questioned but we suppose that it is due to some culture incentives. In the country there is a saying that "for every union a woman should offer a baby to her men", what could be related to these planned pregnancies at a younger age [35, 36]. In STP prevails a culture aspect that promotes young girls into believe that, by conceiving a child, they will be bond to their partner having access to a better quality of life and to a social upgrade.

Sexual education and family planning also needs to be reinforced in the country as we can identify some important gaps. For example, among girls who want to prevent a future pregnancy, they prefer using traditional, rather than modern contraceptives that are provided free of charge, implying a poor knowledge of contraception efficacy [28]. In matters of family planning, it should be noticed that 30% of the adolescents enrolled in this study were already in their second or third pregnancy and that 13.4% had experienced a previous abortion, which are similar results to those obtained in other countries and translate a lack of family planning [46]. Family planning services in STP should actively follow-up these high-risk adolescents to prevent further early pregnancies.

On the other hand, missing opportunities during ANC service in STP can be perceived through this study due to lack of knowledge of adolescent girls in the identification of the newborn's dangers signs in comparison to the older women group, with a statistically significant difference. Therefore, one strategy to overcome this problem is using the ANC attendances to provide, particularly to the teenage pregnant girls, information regarding newborn care and awareness of disease signs and symptoms [47].

School attendance in preventing teenage pregnancies is a key strategy [23, 48, 49]. In our study, educational level was similar among groups and most participants were classified as having elementary school, meaning they didn't attend secondary school, what is usually done from the age of 12 years. Our data are in accordance with other studies in STP that have shown that only 31.1% of adult women reach a secondary level of education and that female participation in the labour market is 41.3% compared to 75.4% for men [27]. Adolescents who are out of school are denied access to comprehensive sexual education and skills needed to negotiate sexuality and reproductive options and prevent pregnancy [48].

To highlight that most adolescent girls in this study were neither studying nor working at the time they got pregnant. Paradoxically, those who were students, had to dropped out from school due to the government disciplinary act prohibiting pregnant girls in the third month of pregnancy from attending classes or school activities [35, 36]. The same sanction was applied to male students involved in the pregnancies. Recently, in 2020, Sao Tome and Principe took a big step to make its education system more equitable and the government revoked this sanction to pregnant young girls and boys [23, 29, 30].

Enhancing adolescents' education through school sexual education programmes in the country should be encouraged, as it can boost their knowledge and their skill to make autonomous decisions, to use contraceptives, to plan to start their own family and to be pregnant later on [10, 23, 45].

Delaying adolescent childbearing in Sao Tome and Principe demands focusing on its major underlying factors: debut of first sex, marriage, and effective contraceptive use—along with the social, cultural, and economic background surrounding these behaviours, remarkably girls' education and gender inequality [50–57].

Study limitations

This study has some limitations. HAM is a reference hospital located in an urban area. This limits its accessibility to women in rural areas and with low socioeconomic

level, thus providing a selection bias. Other significant limitation is that we only identified eight adolescent girls with age ≤15 (very early adolescent childbearing subgroup), although pregnancy in early ages is rare, this small sample could have an impact in the analyses of all the differences between adolescent subgroups.

Other behavioural, social, economic, and family related factors that affect adolescent pregnancy could not be addressed in this study and are a possible future research area, such as: previous family history since adolescent pregnant girls tend to present a positive family history of adolescent pregnancy, mainly in their mothers [8, 12, 18]; girls' parents' education and parent to child communication on sexual reproductive health issues [8]. Behaviour and emotional factors towards an early pregnancy as negative feelings, not knowing the facts about sexual risk, expectations, option of abortion, peer pressure, partner reaction, family support, and a declared intent to become pregnant at a younger age should also be further investigate.

As this study addressed a sensitive subject matter, it could have had the potential of making adolescents or older women uncomfortable in answering some questions, therefore, there could have the possibility of some incorrect answers; however, a high level of confidentiality was maintained during the interviews to ensure that pregnant women were at ease in giving their responses.

Confusing and misleading information on basic health issues as safe period, painful menses, puberty maturational problems, emergency contraception and newborn health were mentioned by girls as major problems in other studies and these subjects should be reinforced in health care visits [1].

Conclusions

Many adolescents in Sao Tome and Principe seem to be experiencing an unplanned pregnancy in the first two months after the beginning of their union/relationship and have a higher probability of not having the baby's father support, being single, student, having no job and lacking appropriate knowledge of identifying newborns' danger signs in comparison to older women. Vulnerability issues as having a sexual life with no previous contraceptive use were also observed. Other concerns, raised by this study, are the age gap difference between young pregnant adolescents and their sexual partners, polygamous relationships, previous abortions and having other living children without the intention to future adopt any contraceptive methods.

Lack of family planning was recognized as a major problem for all the participants, regardless of their age. Thus, providing proper family planning in the country should be urgently reinforced, as it is the key for reducing health, social and psychological costs of unplanned pregnancies, mainly in adolescents.

This can only be done by simultaneously implementing school programmes on sexual education targeting boys and girls with raising awareness of birth control responsibility, namely the use of effective contraceptive methods that should be available to them. Promotion of teenagers' decision-making processes must focus on both genders, and girls' and boys' sexual education should be optimized not only in schools but also through media as radio and television programmes or digital content as mobile apps. Another strategy is to implement programs that promote parent-teenage girls and boys communication of reproductive health issues, starting from early ages, in order to build skills to prevent pregnancy in the late teenage years [50].

Since adolescent sexuality is a culturally sensitive issue, policies that acknowledge the needs of each age-group and programs built with adolescent input that are locally appropriate should be encouraged (https://www.un.org/en/development/desa/population/publications/pdf/popfacts/PopFacts_2019-1.pdf).

None of these interventions will be truly successful in Sao Tome and Principe if the government doesn´t improve, meanwhile, girls' access to adequate living conditions, gender equality and enhance their economic status, ending the cycle of poverty that most are doomed to live and to pass-on to the next generation.

Contribution of our study to knowledge

No study on this subject has previously been published on the socio-demographic and obstetric history differences between adolescents' subgroups and comparing them to older women. The proposed study is the first comprehensive in Sao Tome and Principe, integrating a multivariate analysis in explaining who the adolescents at risk for early pregnancy are in Democratic Republic of Sao Tome and Principe.

Abbreviations

STP: Democratic Republic of Sao Tome and Principe; HAM: Hospital Dr. Ayres de Menezes; OR: Odds Ratio; CI: Confidence Interval; SDG: Sustainable Development Goal; ANC: Antenatal care; DHS: Demographic and Health Survey; MICS: Multiple Indicator Cluster Survey; WHO: World Health Organization; UNFPA: United Nations Population Fund.

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Authors' contributions
AV involved in conceiving the idea of the study, participated in its design, data analysis and interpretation, writing the manuscript and managing the overall progress of the study. MCM and FP involved in study design, data analysis and in revising the manuscript. NB and SS were involved in the study design. The final manuscript was read and approved by AV, MCM, FP, NB and SS.

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Availability of data and materials
The datasets used and/or analysed during the current study are not publicly available in order to ensure participants' privacy and confidentiality but are available from the corresponding author on reasonable request, with the permission from the Director General of Health, Sao Tome and Principe.

Declarations

Ethics approval and consent to participate
Ethical clearance was obtained from the Democratic Republic of Sao Tome and Principe Ministry of Health and Hospital Dr. Ayres de Menezes. Written informed consent was obtained from all participants (or their parent or legal guardian in the case of adolescent under 16) after the purpose of the research was explained orally by the investigator.
This was done only after delivery to reduce coercion due to labour pains. Participation in the survey was voluntary as participants could decline to participate at any time during the study. All methods were performed in accordance with the relevant guidelines and regulations in practice.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Adolescent pregnancy in Sao Tome and Principe: are there different obstetric and perinatal outcomes?

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Abstract

Background: Adolescent childbirth is a major public health problem in Sao Tome and Principe (STP). Adolescent pregnancy and childbirth can carry a risk of morbidity associated with the physiological and sociological characteristics of teenage girls. This study aims to identify the main adverse obstetric and perinatal outcomes for adolescent pregnancies in the Hospital Dr. Ayres de Menezes (HAM), the only hospital in STP.

Methods: An institution-based cross-sectional study. Pregnant women ≤ 19 years of age ($n = 104$) were compared to non-adolescent women ($n = 414$). The obstetric and perinatal outcomes were compared between groups using the t test. Odds ratio (OR) were calculated through Cochran's and Mantel–Haenszel statistics test for odds ratio equal to 1, 95% confidence intervals (CI) and p values ($p < 0.05$) were considered significant.

Results: The adverse perinatal outcomes imputable to adolescent births were foetal distress with low first minute Apgar score < 7 (OR 1.94, 95% CI 1.18–3.18, $p = 0.009$) and performance of neonatal resuscitation manoeuvres (OR 2.4, 95% CI 1.07–5.38, $p = 0.032$). Compared to older mothers, teenage girls were likely to have a non-statistically significant threefold higher risk of having an obstructed labour (OR 3.40, 95% CI 0.89–12.94, $p = 0.07$). Other perinatal outcomes as neonatal asphyxia, risk for cerebral palsy, premature birth, early neonatal infection, and neonatal death were identical between groups as well as maternal anaemia, mode of delivery or other obstetrical outcomes.

Conclusion: Adolescent pregnancies were associated with worse perinatal outcomes as foetal distress and higher need for neonatal resuscitation manoeuvres. This study may support STP health authorities in their efforts to make Sustainable Development Goals 3 (good health and wellbeing), 4 (quality education) and 5 (gender equality) a reality by 2030, since it identifies specific problems that need to be addressed to improve maternal adolescent health.

Keywords: Antenatal care, Adverse pregnancy outcomes, Adolescent pregnancy, Sao Tome and Principe

Background

Adolescence is a stage of life that enables growth, development and behaviour optimization that sets a baseline for health in later life and for the next generation [1]. Adolescent girls (age ≤ 19 years at time of delivery) give birth to approximately 16 million babies each year, nearly 11% of births worldwide, being a global challenge linked with maternal and child morbidity and mortality that affects the socio-economic development of a country [2–5].

In Africa, adolescent pregnancies are a major public health issue as it is estimated that 33% of teenage girls give birth before the age of 18 and 3.5% even before the age of 15 years [2]. Low resource-constrained countries

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urge to reduce this public health imperative to reach the Sustainable Development Goals (SDG) by 2030 [6]. This is essential as adolescent pregnancies indirectly act as a drawback to the attainment of these goals [4] as they are at risk of socioeconomic hardship, poverty, out of school (Goal 1, 2 and 4) and to die from pregnancy-related complications (Goal 3) [4, 7–12].

Research suggests that adolescent girls compared to older women have higher risks of inadequate antenatal health care (ANC), cephalopelvic disproportion, obstructed labour, and death during pregnancy and childbirth [12–16]. Adolescent girl's height and pelvic dimensions are only complete by two years after menarche, which can be linked to a higher risk for cephalopelvic disproportion and consequently to have an obstructed labour [14, 15]. To notice that obstructed labour is one of the most frequent and preventable causes of maternal and perinatal mortality and disability and a concern among teenage pregnancies [14].

Adolescent pregnancy can also be a risk to the baby [17–21]. There is substantial reason for arguing that adolescent´s newborns are more likely to be stillbirth, to die before they are one month old [21, 22], have low Apgar score [12, 21, 23], low birth weight (LBW) [21, 24] and to be admitted to an intensive care unit [21, 25].

Other adverse pregnancy outcomes are controversial in literature such as caesarean section, vaginal instrumental delivery, postpartum haemorrhage, and preeclampsia [26–30].

Some authors consider that adolescent child bearers are not a high-risk group if good ANC is provided [21, 31, 32] and Lawlor et al. [33] held that there is no biological reason to suggest that having a baby before the age of 20 is associated with higher risk for disability or mortality.

The evidence is controversial, as debate continues in whether the associations observed are related to the adolescent biological immaturity or were confounded by their lack of health care and frequently poor socioeconomic conditions [32–38]. Other factors have also been mentioned in the literature as explanations for this conflicting evidence, namely 1) heterogeneity of study settings (hospital-based vs population-based studies); 2) small sample sizes, mainly for adolescents < 15 years and 3) different conceptual approaches to adjust for potential confounders [32, 33].

Sao Tome and Principe (STP) is the second smallest sub-Saharan country but has one of the highest adolescent pregnancies prevalence in the region reaching around 27% [39]. There is, however, a knowledge gap concerning the obstetric and perinatal characteristics of this major public health problem in this country. The authors have also studied these pregnant adolescents´ characteristics and factors associated with early childbearing in STP, whose results were published in another article [40].

In the present study, we sought to identify the main adverse obstetric and perinatal outcomes for these adolescent pregnancies.

Material and methods

Study design

This is a cross-sectional analytical hospital-based study and data was collected among eligible study participants between July 2016 and November 2018.

Study context

The study was conducted in Hospital Dr. Ayres de Menezes (HAM) in Sao Tome, the country´s capital, a growing city with 64% of the country population living in it [41, 42]. It is a high-volume low-resource hospital, with a maternity ward delivering around 82,4% of all the deliveries in the country with an average of 8 to 12 deliveries per day [39, 43].

The Democratic Republic of Sao Tome and Principe is a country with two islands in the Gulf of Guinea, in the western equatorial coast of Central Africa [39]. Women of childbearing potential represent about a quarter of the population and the number of expected pregnancies is around 5,000 per year [41–43]. The country´s maternal mortality ratio shows considerable progress from 158.3 maternal deaths per 100,000 live births to 74 per 100,000 live births in 2014, but the reduction was not enough to meet the Millennium Development Goal number five [41–43]. Antenatal health care is generally available in the country, with 98% of women being attended at least once by a skilled health provider during pregnancy [41, 42]. The coverage rate for at least four antenatal visits was 72% in 2009, rising to 84% in 2014 [41, 42]. STP level of poverty is high, with 66.2% of the population living on less than two euros per day, which is a major obstacle to achieve universal coverage [39, 41]. Antenatal consultations are free, but women pay around twenty euros for all mandatory routine tests.

Comprehensive emergency obstetric care (caesarean sections and blood transfusions) is only available at the maternity ward of HAM, the only hospital in the country. High-risk patients are routinely referred to the HAM before, during labour, or after birth. At the maternity ward, the ratio of skilled midwives to deliveries is often one to three deliveries. In the daytime there are usually two obstetricians for performing the vaginal instrumental deliveries, caesarean sections, or other obstetric complications and on the night shift only one of them remains at HAM. Intrapartum foetal monitoring at HAM consists of a five-minute cardiotocography approximately

every two hours and indication for restricted episiotomy during delivery depends on individual risk factors and obstetric conditions, as advocated by World Health Organization (WHO) [44]. Partograph and birth records are filled by the midwives. Neonatal resuscitation including suction, oxygen by bag and mask and cardiac massage follows the WHO standard procedures and is undertaken by the midwives. There is a Neonatal Care Unit (NCU) for term and premature newborns with six cots with no facilities for assisted ventilation.

Study population and sampling

Participants were enrolled at HAM maternity ward after pregnant women admission for the baby´s delivery, there was a mean of 4540 deliveries during the study period.

Sample size was calculated using the WHO-steps approach [45] using a web based freely accessible sample size calculator, Raosoft® (http://www.raosoft.com/samplesize.html). Based on the formula for sample size and margin of error from the software, the minimum sample size was S = 355, which placed the right dimension between 355 (95%) and 579 (99%) confidence. For the original study, a total of 518 participants were enrolled for the study based on the following assumptions: two-sided 95% confidence level, power of 80% to detect an odds ratio of at least 2 for adverse birth outcomes. This sample size was also supported by PASS® software (https://www.ncss.com/software/pass/). Since, the sample size was not calculated for present outcomes, a power analysis was performed, varying from 63% to 87% for outcomes as neonatal resuscitation and foetal distress for this study.

The eligibility criteria for participants were: 1) prepartum women, 2) prepartum adolescents (under ≤ 19 years) who had obtained permission from their parent/s or legal guardian/s to participate in the study and 3) women and adolescents who gave birth outside the hospital but were admitted for postpartum care. The exclusion criteria included: 1) adolescents under 13 years of age; 2) adolescents who had not obtained permission from their parent/s or legal guardians to participate in the study; 3) adolescents with cognitive impairment; and 4) those admitted for abortion (gestational age < 28 weeks). None meet the exclusion criteria.

A random sampling was applied to recruit the study participants. Each morning, from the pile of mothers´ medical folders, we selected every second interval folder and then carry on asking for her consent for enrolment. The study was done at different months (two weeks every two other months) to avoid seasonal interference (rain season and malaria period), avoiding effects by means of confounding variables by guaranteeing a sample with few biases.

Five hundred and eighteen women aged 14–49 years consented to participate were included. The pregnant women were divided into two groups, ≤ 19 years old versus older > 19 years. Pregnancies that occur in a girl ≤ 19 years of age are referred to as an adolescent or teenage pregnancy. There were 104 pregnancies in women aged ≤ 19 years (adolescent group) and 414 in women more than 19 years (older women group). Participants (adolescents vs older counterparts) were also divided into primiparas (those having their first delivery) and multiparas (those having their second or above delivery) and the proportions of the complications were compared using Fisher's exact test.

Variables

In relation to the number of births they were classified as nullipara (para 0), primipara (para 1) or multipara (> para 1). ANC consisting of less than four consultations during pregnancy was considered as inadequate, between 4–7 as adequate and 8 or more visits as complete.

Gestational age was estimated from the date of onset of the last normal menstrual period, since the ultrasound dating of pregnancy is not usually done in this setting, although recommended during ANC consultations. Obstetric ultrasound was assessed in this study with the total number of scans per participant as well if performed before the 20th week of pregnancy (early obstetric ultrasound).

Maternal outcomes investigated were: (i) anaemia during pregnancy (haemoglobin concentration < 11 g/dl), (ii) preeclampsia (hypertension ≥ 140/90 mmHg and proteinuria in dipsticks in women who were normotensive at ANC), (iii) perineal tear, (iv) episiotomy, (v) caesarean section, (vi) assisted vaginal delivery (only performed by vacuum in HAM), and (vii) post-partum haemorrhage (> 500 mL bleeding). A diagnosis of pre-labour rupture of membranes (PROM) was made on clinical examination. Obstructed labour was operationally defined as the sum of all caesarean sections due to mechanical problems or foetal distress and all instrumental delivery.

Data about labour, delivery and its complications were collected from the partograph. Partographs tend to represent the monitoring of four parameters: 1) foetal heart monitoring, 2) uterine contractions, 3) blood pressure, and 4) pulse. A checklist was used to verify the correct use of partograph by the midwives (complete vs incomplete) in monitoring the four parameters mentioned above. We also review labour and delivery notes and supplemented with neonatal records.

The evaluated perinatal outcomes were: (i) prematurity, defined as a live infant delivered before 37 completed weeks of gestation from the date of onset of the last normal menstrual period, (ii) post-term labour, gestational

period beyond 40 completed weeks as a prolonged pregnancy, (iii) low birth weight, newborn weight less than 2500 g at birth, (iv) large birth weight when ≥ 4000 g (macrossomia), (v) foetal death (dead infant after 28 weeks' gestation) and (vi) admission at the Neonatal Care Unit.

Birth asphyxia was determined using the components of the APGAR score table [46], since techniques as umbilical arterial blood gas samples from a clamped section of the umbilical cord aren´t available in STP. The score comprised five components, which were appearance (colour), heart rate, grimaces (reflexes), activity (muscle tone), and respiration. A score of 0, 1 or 2 was given to each component. For this study the definition of (i) foetal distress was a low Apgar score < 7 at the first minute of life, (ii) clinical asphyxia was considered in infants with a 5-min Apgar score < 7 [47] and (iii) assessment of severity was defined as risk for cerebral palsy with an Apgar score of 5 or less at 5 min [46, 47]. This was similarly applied to both term and preterm infants.

Data collection

Data on prepartum, intrapartum and postpartum characteristics of participants, were gathered and collected from 1) antenatal card, 2) obstetric maternal hospital and 3) newborn's records. For prepartum data, relevant details of the perinatal history and antenatal period were collected systematically from the antenatal pregnancy cards. For intrapartum and postpartum data, mothers' and newborns' medical hospital records were collected. Socio-demographic data were obtained through a face-to-face interview of the mothers, 12–24 h after delivery, using a structured questionnaire. The questionnaires were performed in Portuguese, the national language. The principal investigator (a paediatrician) executed and was responsible for all main activities as: 1) obtaining consent and enrolment of the participants, 2) data collection from antenatal cards plus maternal clinical and newborn's records, 3) newborns` clinical exams (for diagnosis confirmation), 4) face-to-face interviews and 5) data collection entry in the database.

Data management and statistical analysis

Data was secured in a confidential and private location. Participants were referred to by identification numbers and the informed consent forms were kept separate from the questionnaires. Both could only be linked by a coding sheet available only to the main investigator. Administered questionnaires were checked for completeness and consistency.

Data analysis in this study was carried out with the associations between maternal ages categorized as adolescent mothers (1) vs others (0). Each maternal and neonatal complication was assessed with Mantel = Haenszel Common Odds Ratio (OR) Estimate that was developed, resulting in the calculation of OR, 95% confidence intervals (CI) and p-values. For each outcome with a statistically significant difference at the first level, further analysis was developed using mothers´ age as a continuous variable with adjustment made simultaneously for the following factors, independently of their statistical significance: ultrasound and antenatal care. For statistical purposes, maternal age was kept as a continuous variable in the models. Mean age of the mothers was 26.59 years (sd 7.1) with a quasi-normal distribution, just underrepresented at the very young mother's level. Two step logistic regression models were developed to assess the power of age as a predictor. The models were adjusted for marital status, education and antenatal care, the probabilities of event were recorded for each case and the plots obtained with the respective 95% CI for each age point.

Regarding confounding variables, multivariate logistic regressions were performed in two stages—first with only the variable under study (mother's age) and then including control variables to understand whether the identified effect occurred via other variables (education, presence of the partner and antenatal care).

Statistical significance was defined as $p < 0.05$. Data were analysed with SPSS software, version 26.0 (SPSS for Windows, Chicago, IL: SPSS Inc., 2020).

Ethics approval and consent to participate

Approval to carry out this study was obtained from the Democratic Republic of Sao Tome and Principe Ministry of Health and Hospital Dr. Ayres de Menezes. Written informed consent was obtained from every participant (or their parent or legal guardian in the case of teenagers under 16) after the purpose of the research was explained orally by the investigator. Participation in the survey was voluntary, as participants could decline to participate at any time during the study. Anonymity and safety of participants were ensured. All methods were performed in accordance with the relevant guidelines and regulations in practice.

Results

There were 104 pregnancies in adolescents (≤ 19 years) in 518 hospital deliveries and 414 in older women. The rate of adolescent pregnancy was 20.1% (CI – 16,3% to 23%), with a mean age of 17.42 years, median 17 with a minimum age 14 years old. Adolescent ages were: 1% (1) 14 years old, 7% (7) 15, 19% (20) 16, 24% (25) 17, 20% (21) 18 and 29% (30) 19 years old.

The older women group mean age was 28.9 years old, median 28 with a maximum age of 43. Regarding the adult group, the mother´s mean age at first pregnancy was 20.1 (± 3.76 SD) years (minimum 13, maximum 36).

Intrapartum: antenatal characteristics and complications

Characteristics and complications in the antenatal period are described in Table 1. There was no maternal death in the study.

A first attendance at the antenatal care facility before the 12th week of pregnancy was performed by 60.9% (63) of the adolescent group and by 52.8% (219) of the adult group.

The date of onset of the last menstrual period was not acknowledged by 8.7% (9) of the adolescents and by 12% (50) of the adult women group (OR 0.69, 95% CI 0.32–1.46, $p = 0.335$) which is considered not to be statistically significant.

There was no significant statistical difference between the two groups regarding the antenatal care: i) all adolescents (104) and (413) in the older women group were attended at least once by a skilled health provider during pregnancy; ii) inadequate ANC (0–3 visits) was observed in 14.4% (15) of the teenager group and 13.3% (55) in the older women (OR 1.1, 95% CI 0.6–2, $p = 0.76$); iii) adequate ANC (4–7 visits) was observed in 43.3% (45) of the adolescent group vs 47.3% (195); iv) complete ANC (> 8 visits) was verified in 42.3% (44) of adolescents and 39.4% (159) in older women; v) minimum of four visits in this pregnancy was observed in 85.4% (88) of the teenage group vs 86.4% (88).

One ultrasound scan was performed in 48.1% (49) of the adolescent pregnancies and 60.4% (248) in the control group (OR 0.61, 95% CI 0.4–0.9, $p = 0.024$). Two ultrasound scans were performed in 8.7% (9) of the adolescent pregnancy and 14.9% (59) in their older counterparts (OR 0.55, 95% CI 0.263–1.15, $p = 0.376$). Ultrasound scan before 20 weeks' gestation (early ultrasound) was made in 41.7% (43) of the adolescents and 49% (98) in the older women group (OR 0.74, 95% CI 0.4–1.4, $p = 0.30$).

Although the analysis of adolescents versus older women seemed to point towards a difference in the probability of ultrasound during pregnancy that seems not to be the case when we extend the analysis of age as a continuous variable (Fig. 1). Most women have a probability slightly above 50%, while younger women seem to be just a little less likely to perform this exam. The variable age loses power to the control variable antenatal care. Women who are well followed during pregnancy have a higher probability of getting an ultrasound scan (OR 1.8, $p = 0.004$) independently of their age.

Comparison between primiparas and multiparas for both groups (adolescents vs older counterparts) revealed that the proportions of the complications were similar for both groups.

HIV and syphilis were not found in any adolescent compared to the adult group with 0.8% (4) and 1% (5) respectively. Malaria was diagnosed in 0.4% (2) of the teenage group vs 0.2% (1) in the older group. There is no statistically significant difference between groups.

Table 1 Antenatal characteristics and complications

Characteristics	Adolescent pregnancies $n = 104$ (%)	Other pregnancies $n = 414$ (%)	OR	CI	*p* value
Primigravida*	73 (70.2%)	54 (13%)	15.7	9–26	≤ 0.001
Inadequate ANC (< 4 visits)	15 (14.4%)	55 (13.3%)	1.1	0.6—2	0.76
Preterm labour	10 (9.6%)	43 (10.4%)	0.98	0.4 – 1.9	0.82
PROM	9 (8.6%)	33 (7.9%)	1.1	0.5 – 2.4	0.83
Malpresentation	2 (2.2%)	6 (1.7%)	1.3	0.3—6.4	0.77
Past dates	13 (12.4%)	66 (15.3%)	0.77	0.4 – 1.5	0.42
Preeclampsia	10 (9.6%)	27 (6.5%)	1.55	0.71–3.26	0.27
Preeclampsia in nulliparous	7 (8.3%)	2 (2.9%)	3.0	0.60–14.94	0.18
Obstructed labour**	13 (12.5%)	42 (10%)	3.40	0.89–12.94	0.07
Anaemia	31 (42.5%)	135 (41.3%)	1.8	0.7—5	0.24
Rh incompatibility	3 (5.5%)	16 (5.7%)	1.05	0.3 – 3.7	0.94
IUGR	3 (2.9%)	17 (4.0%)	1.05	0.3—3.6	0.93

* The proportion of primigravidas was higher in the adolescent group (OR 15.7, 95% CI 9–26, p ≤ 0.001) as compared to the older women as well as for nulliparous with 80.6% (83) in the first group and 16.3% (65) in the latter

** Compared to older mothers, adolescent mothers are likely to have a non-statistical significance of a threefold higher risk of having an obstructed labour

Abbreviations: *PROM* pre-labour rupture of membranes, *IUGR* Intrauterine growth restriction, *OR* Odds Ratio, *CI* Confidence interval

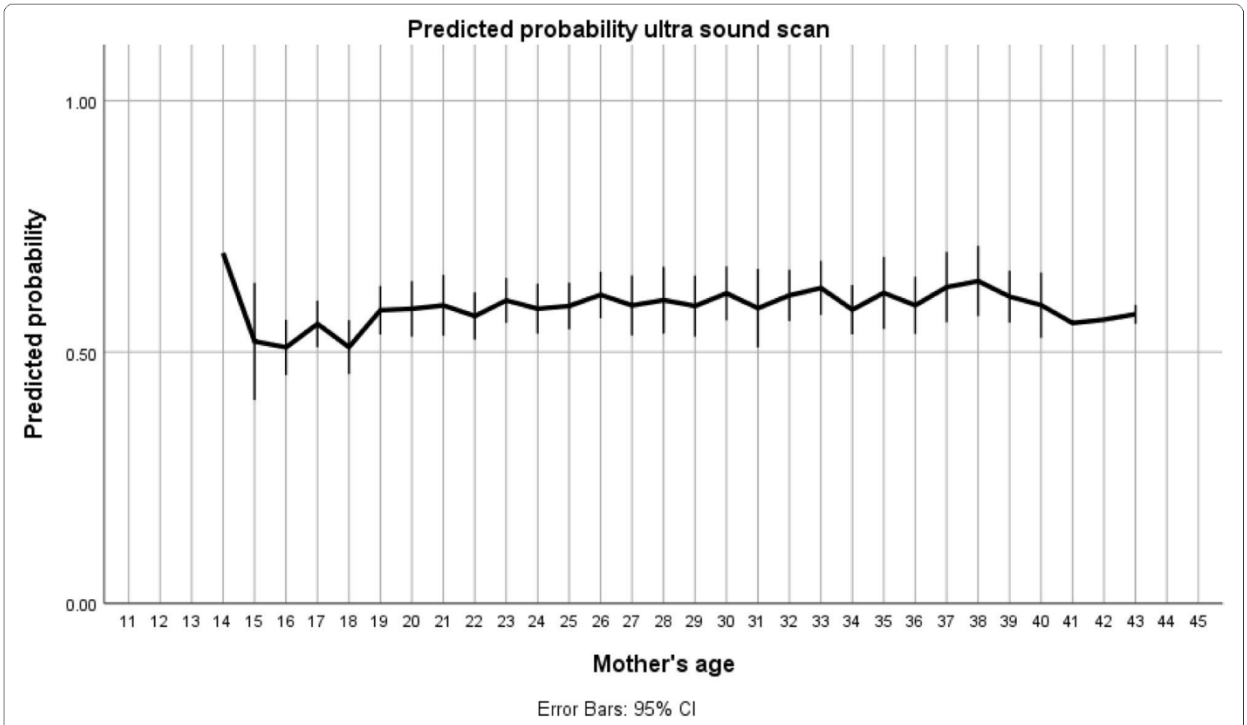


Fig. 1 Probability of having an ultrasound during pregnancy according to mother´s age. * Analysis with age as a continuous variable. The model was adjusted for marital status, education, and antenatal care. The line at 0.5 represents equal probability of ultrasound

Table 2 Mode of delivery and its complications

Characteristics	Newborns from adolescents' mothers *n* = 105 (%)	Newborns form older women *n* = 430 (%)	OR	CI	*p* value
Normal vaginal delivery	89 (84.8%)	361 (84%)	1.14	0.6–2.1	0.67
Caesarean section	12 (11.4%)	69 (16%)	0.675	0.351–1.3	0.24
Assisted vaginal delivery	4 (3.8%)	6 (1.4%)	2.8	0.8 – 10.1	0.11
Episiotomy*	17 (16.2%)	28 (6.5%)	2.8	1.5—5.4	0.002
Perineal tear	5 (5.5%)	9 (2.3%)	2.5	0.81 – 7.5	0.11
Postpartum haemorrhage	3 (2.9%)	8 (1.9%)	1.6	0.41 – 5.9	0.51

* When adjusted the predicted probability of episiotomy is reduced to near zero with age, with teenagers having a probability of about 0,2 (Fig. 2)

Abbreviations: *OR* Odds Ratio, *CI* Confidence interval

Intrapartum: mode of delivery and its complications

The mode of delivery and its complications are described in Table 2.

Home was the place of delivery for 4.1% (3) adolescents and for 2.5% (11) of the older pregnant (OR 1.663, 95% CI 0.5–5.4, $p = 0.39$).

Regarding the partograph register by midwives (during labour and delivery) both groups had an incomplete registration in 80% of the partographs. Midwives' observations and monitoring were only recorded in a dismal 5% of cases, as per accepted frequency, as follows: foetal heart monitoring and uterine contractions 20%, blood pressure 14% and pulse 8%.

The practice of episiotomy was significantly higher in teenage pregnancies 16.2% (17) as compared to 6.5% (28) in the older women group (OR 2.8, 95% CI 1.5–5.4, $p = 0.002$) as observed in Table 2. Nevertheless, the probability is reduced to near zero with age, with young women having a probability of about 0,2 (Fig. 2) after adjusting for primiparas. The overall probability of episiotomy was generally low.

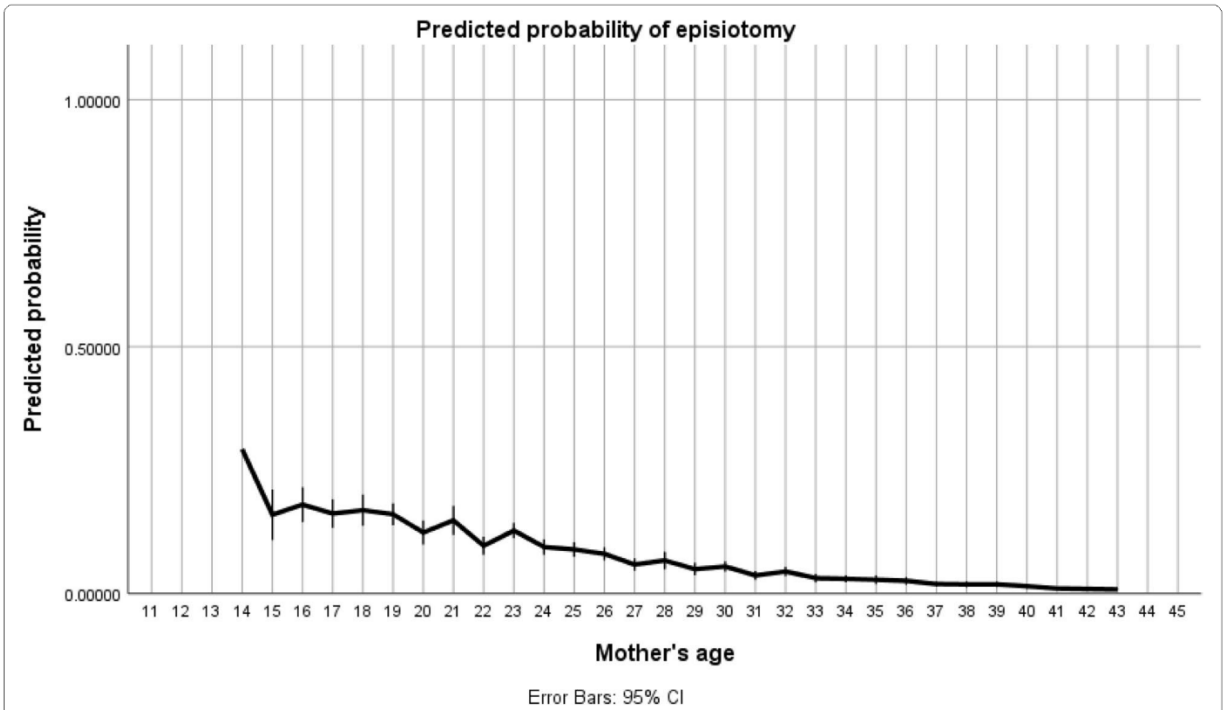


Fig. 2 Predicted probability of episiotomy. *The model was adjusted for primiparas, marital status, education, and antenatal care. The line at 0.5 represents equal probability of episiotomy.

Table 3 Perinatal outcomes

Characteristics	Newborns from adolescents' mothers $n = 105$ (%)	Newborns form older women $n = 430$ (%)	OR	CI	*p* value
Stillbirth	2 (1.9%)	14 (3.3%)	0.58	0.13 -2.6	0.47
Foetal distress*	30 (29.4%)	73 (17.7%)	1.94	1.18–3.18	0.009
Birth asphyxia	11 (10.9%)	31 (7.5%)	1.5	0.72–3.10	0.27
Risk for cerebral palsy	4 (3.9%)	9 (2.2%)	1.82	0.55–6.05	0.32
Neonatal resuscitation**	10 (9.5%)	18 (4.2%)	2.4	1.07–5.38	0.032
Infectious risk	19 (18,1%)	78 (18.1%)	0.99	0.6 – 1.7	0.99
Large gestational weight	1 (1%)	20 (4.7%)	-	-	-
Low birth weight	19 (18.3%)	81 (19.5%)	0.95	0.55–1.7	0.98
Congenital anomalies	3 (2.9%)	7 (1.6%)	1.8	0.5 – 6.9	0.41
Admission at NCU	15 (18.5%)	51 (13.9%)	1.4	0.74–2.64	0.29

* There was a statistically significant difference between the two groups regarding foetal distress with low Apgar score (< 7) at the first minute of life, with 29.1% (30) in the adolescent group and 17.8% (74) in the older women group (OR 1.94, 95% CI 1.18–3.18, p = 0.009)

** Neonatal resuscitation was performed more often in babies born from adolescent mothers 9.5% (10) compared to 4.2% (18) of the adult group (OR 2.4, 95% CI 1.07–5.38, $p = 0.032$)

Abbreviations: *NCU* Neonatal Care Unit, *OR* Odds Ratio, *CI* Confidence interval

Postpartum: perinatal outcomes

Perinatal outcomes are described in Table 3.

Comparisons of pregnancy outcomes between very early (14–15 years), early (16–17 years) and late adolescence (18–19 years) found no significant differences. No difference was found in the comparison with women ≥ 35 years old. There was no significant difference between the two groups regarding other antenatal, delivery or newborn complications.

Discussion

Pregnancy at an early age is regrettably common in many low-income countries and yet the debate about the degree of the associated maternal and perinatal risk is still open. Adolescent pregnancy is recognized as an important social and health concern in Sao Tome and Principe because it is often a trajectory in life steeped in social inequalities with adverse obstetric and perinatal outcomes [48, 49]. Through this study we aimed to identify if adolescent pregnant women had specific adverse outcomes when compared to older counterparts.

The adolescents age distribution findings revealed that those aged 14–15 years accounted for the least proportion (8%) of the study population, probably due to less developed secondary sexual characteristics in these younger teenagers. Still, this 8% rate of pregnancies in girls before the age of 15 years is two times higher to the 3.5% published for Africa [2]. On the other hand, almost 50% of the adolescent girls were aged 18 and 19 years old, which may be responsible for the few adverse outcomes identified in this study.

Most of the adolescents were primigravidas, what is expected, and which is also seen in similar studies [50]. Several studies have highlighted the importance of antenatal care in reducing the risks of adverse outcomes during pregnancy [21, 31–36]. The few adverse outcomes among adolescents reported in this study may be due to the high rates of ANC coverage in the country as all adolescents and older women were attended at least once by a skilled health provider during pregnancy. Comparing STP to other sub-Saharan African countries, the proportion of adolescent women who had accessed ANC at least once ranges from 29% in Ethiopia to 93% in South Africa [51].

A high rate of adolescents (85.4%) and older women (86.4%) had at least four antenatal visits and complete ANC were found in 42.3% of the adolescents, reinforcing a strong structure in ANC service available in the country. In other sub-Saharan countries this proportion drops to 30% in Ethiopia, 35% in Mali and in Guinea and 49% in South Africa [21].

Another positive aspect is that 60.9% of the adolescents had their first ANC attendance before the 12th week of pregnancy contrasting to other studies [21, 50]. According to the WHO, in these countries, young pregnant women come late or not at all for antenatal care, mainly because of inadequate knowledge of its importance, poor family support and due to the fear of a reproving look of the caregiver on an adolescent who is pregnant [49–52].

In STP women who were well followed during pregnancy have a higher probability of getting an ultrasound scan independently of their age. However, it should be highlighted that almost half of the teenagers found the economic resource to do one ultrasound scan reinforcing the health education available.

The rate of obstetric complications in teenagers differs from study to study. In the present study, pregnancies in adolescents were not associated with a higher risk for preeclampsia but we found that young age and nulliparity had a threefold higher risk for preeclampsia, although with no-statistically significant difference (OR 3.0, 95% CI 0.60–14.94, p = 0.18), mainly due to the low number of patients enrolled.

It should be noticed that the delivery of the baby at home happened only in 4.1% of adolescents and in 2.5% of the older woman group. In STP despite limited specialized medical human resources of HAM, births attended by skilled health staff happened in 93% of cases, considerably higher than in other Portuguese-speaking countries, namely 91% in Cape Verde, 68% in Equatorial Guinea, 50% in Angola, 54% in Mozambique and 45% in Guinea-Bissau [53].

Regarding childbirth, some authors suggest that the physical immaturity of the adolescent girl, especially her pelvis, is a factor of dystocia [14, 15]. Similar to our findings, other studies did not find any increase in the caesarean section rates among adolescents [50]. Episiotomy appeared more likely to be done among the adolescent group, possibly due to their developing and rigid perineum but when the model was adjusted, this rate was reduced to near zero. There were also low rates of perineal tear at vaginal delivery in both groups, with a tendency of a twofold higher risk for teenagers (OR 2.5, 95% CI 0.81–7.5, $p = 0.11$) but also with no-statistically significant difference. These data suggest that a better perineal guard in labour at HAM should be thought to minimize perineal tear.

There were no maternal deaths in this study. In STP, there were three cases of maternal deaths reported during the study period, from which two were in the 15–19 age group (adolescent group) and one in the group of 25—29 years [42]. Regarding to 2017 data on maternal mortality rate (MMR), Cape Verde estimates only 43 maternal deaths per 100,000 live births, while STP maintains 73 MMR. Nonetheless, STP´s MMR is lower when compared to the other countries such as Guinea-Bissau with 457, Mozambique 206, Equatorial Guinea 181, and Angola 167 MMR [53].

There was no statistically significant difference in stillbirths born to adolescents or older mothers. This was consistent with findings from other studies where adolescents were just as likely to have stillbirths as older women [2]. In the present study, neonates from adolescent mothers were similarly born at term as those from

their adult counterparts. This finding is contrary to that observed by some authors [8, 12, 54, 55].

We have not found any statistically significant difference concerning congenital malformations in newborns of adolescent girls contrarily to Vinatier et al. [56] that reported more malformations in newborns of mothers under age 15 (21%), than in those from older women.

Our results are opposite to most literature, which show that adolescent pregnancies have poorer neonatal birth outcomes, as prematurity, small for gestational age and stillbirth and neonatal deaths [26–30]. We did not find an association between young maternal age and neonatal morbidity or mortality except for foetal distress and neonatal resuscitation.

Foetal distress and higher need for neonatal resuscitation manoeuvres found in the adolescent group reflect a difficult transition between in-utero to life. This can be probably due to the biological concern that younger women are more likely to have an immature pelvis, as it continues to grow throughout adolescence. This can lead to cephalopelvic disproportion, obstructed labour, or other obstetric complications [15].

We found a weak statistically significant difference ($p = 0.07$) in the adolescent group for a threefold higher risk of having an obstructed labour. This was consistent with results from other studies carried out in Cameron and in other sub-Saharan African countries [8].

Regarding assisted vaginal delivery, we found a twofold higher risk of it being performed in the adolescent group, but also with a no-statistically significant difference ($p = 0.11$), mainly due to the low number of participants enrolled.

This highlights the need for specialist attention for adolescent mothers' labours and a prompt referral to a caesarean section when needed. These obstetric complications can also be reduced by using the partograph to assess the labour progress. Foetal monitoring may provide crucial information on the adequacy of foetal oxygenation during labour for timely and appropriate management of complications. Even though we have found that the partograph sheet was available in all obstetrical records, accurate recording of parameters—to monitor the foetus, the mother, and the progress of labour—was rarely done by the midwives. From our field experience, we can speculate or predict that interventions, such as advocacy for the use of the partograph should be encouraged at the maternity ward of HAM and probably in many other sub–Saharan African hospitals for prevention of foetal distress.

Furthermore, the emotional and psychological needs of pregnant adolescent girls can be greater than those of older women [52]. At HAM there is a complete isolation of the labouring woman from family members, which is unusual in most contemporary labour settings [44, 49]. This factor can worsen the adolescent preparedness to cooperate during the baby's birth. In our opinion, service planners need to offer every pregnant woman privacy, allowing her to be accompanied by a supportive person throughout labour and delivery. An attractive and humanistic setting should be provided since this approach reduces the need for medical interventions and has the potential to encourage greater use of health facilities [22, 44, 52].

Nonetheless, newborns from adolescent mothers did not experience more risks for birth asphyxia nor for cerebral palsy.

Strength and limitation of the study

This study has several limitations. Firstly, the estimation of adverse risks could be biased, as the study was implemented in the country´s only health facility with the capacity to perform caesarean sections. Secondly, the study was carried out in one health facility, in the country's capital, and cannot be used for generalisations for the rest of the country. The results obtained from adolescent deliveries underestimates the burden of adolescent pregnancies in Sao Tome and Principe, as several girls may have had abortions or may have given birth at home and could therefore not be recruited into the study.

Nevertheless, this study allowed us to build the first map-making of the adolescent deliveries situation in Sao Tome and Principe which could help in policy-making and clinical decisions.

This study included a total number of pregnant women similar to the one published by UNICEF in the Multiple Indicator Cluster Survey (MICS) for STP [39]. In contrast to MICS, our study has the advantage of not being vulnerable to memory or recall bias because the data were gathered for the current pregnancy and delivery with data abstracted directly from clinical records and antenatal cards.

Future studies

A future study with a superior number of participants could clarify if the higher tendencies identified in adolescents regarding obstructed labour, assisted vaginal delivery, and preeclampsia in nulliparous are statistically significant, in order to plan a successful intervention.

Contribution of our study to knowledge

No study on this subject has previously been published on the risk factors and the maternal and perinatal prognosis of childbirth in adolescents in Sao Tome and Príncipe. It is the first comprehensive study of this problem in the country, integrating a multivariate analysis to assess maternal and perinatal outcomes.

Conclusions

Adolescents had adverse perinatal outcomes as foetal distress and a higher need for resuscitation manoeuvres of their newborns. Compared to older mothers, adolescent mothers are likely to have a non-statistical significance of a threefold higher risk of having an obstructed labour.

We can also guess the existence of other than age-related factors for foetal distress in adolescent mothers, namely emotional and psychological issues, and difficulties of an unprepared girl to face the labour stages and cooperation during the baby's delivery. Therefore, pregnancies and deliveries among adolescents should be carefully monitored.

The good antenatal care coverage rates shown can be accountable for the few adverse outcomes found for adolescent pregnancies in this study.

To sum up, this study provides a baseline data on the complications among pregnant adolescents in this low resource country and may contribute to the local efforts to make SDG for maternal health a reality by 2030.

Abbreviations

STP: Sao Tome and Principe; HAM: Hospital Dr. Ayres de Menezes; OR: Odds Ratio; CI: Confidence interval; SDG: Sustainable Development Goal; ANC: Antenatal care; MICS: Multiple Indicator Cluster Survey; WHO: World Health Organization; PROM: Pre-labour rupture of membranes; IUGR: Intrauterine growth restriction; NCU: Neonatal Care Unit.

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Authors' contributions

AV involved in conceiving the idea of the study, participated in its design, data analysis and interpretation, writing the manuscript and managing the overall progress of the study. MCM and FP involved in conceiving the study, data analysis and in revising the manuscript. NB and SS were involved in the study design. The final manuscript was read and approved by all the authors.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Approval to carry out this study was obtained from the Democratic Republic of Sao Tome and Príncipe Ministry of Health and Hospital Dr. Ayres de Menezes. Written informed consent was obtained from every participant (or their parent or legal guardian in the case of teenage under 16) after the purpose of the research was explained orally by the investigator. Participation in the survey was voluntary, as participants could decline to participate at any time during the study. Anonymity and safety of participants were ensured. All methods were performed in accordance with the relevant guidelines and regulations in practice.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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RESEARCH ARTICLE

Antenatal screenings and maternal diagnosis among pregnant women in Sao Tome & Principe—Missed opportunities to improve neonatal health: A hospital-based study

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Abstract

Newborn mortality and adverse birth outcomes (ABOs) in Sao Tome & Príncipe (STP) are overwhelmingly high, and access to quality-antenatal care (ANC) is one of the strategies to tackle it. This study aimed to fill the gaps in ANC screenings with a focus on how to improve neonatal outcomes. We conducted a retrospective hospital-based study in which ANC pregnancy cards were reviewed. Screenings were described and compared according to the total number of ANC contacts: 1–3 (inadequate), 4–7 (adequate), and ≥8 (complete). The collected data were entered into QuickTapSurvey and exported to SPSS version 25 for analysis. Statistical significance was considered at a p-value ≤0.05. A total of 511 ANC pregnancy cards were reviewed. Mothers' mean age was 26.6 (SD = 7.1), 51.7% had a first trimester early booking, 14.9% (76) had 1–3 ANC contacts, 46.4% (237) had 4–7 and 38.7% (198) >8. Screening absence was found in 24%-41%, lack of money was registered in 36%. Pregnant women had no screening performed for HIV in 4.5%, syphilis in 8.8%, HBV 39.3%, malaria 25.8%, hemoglobin 24.5%, blood glucose 45.4%, urine 29.7%, stool exams 27.8% and 41.1% had no ultrasound. Screening completion for blood group, HIV, malaria, urine, hemoglobin, and coproparasitological exam were found to have a statistically significant difference ($p<0.001$) for the complete ANC group when compared to other groups. Antenatal problems identified were: 1) bacteriuria (43.2%); 2) maternal anemia (37%); 3) intestinal parasitic infections (59.2%); 4) sickle cell solubility test positive (13%); and 5) a RhD-negative phenotype (5.8%). Missed-ANC treatments were up to 50%. This study reveals a coverage-quality gap in STP since no pregnant woman is left without ANC contact, although most still miss evidence-based screenings with an impact on neonatal outcomes. Strategies such as implementing a total free ANC screening package in STP would enhance maternal diagnosis and prompt treatments.

Data Availability Statement: The datasets used and analyzed during the current study are all available within the manuscript itself.

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Competing interests: The authors have declared that no competing interests exist.

Abbreviations: STP, Sao Tome and Principe; HAM, Hospital Dr. Ayres de Menezes; SDG, Sustainable Development Goal; ANC, antenatal care; MICS, Multiple Indicator Cluster Survey; WHO, World Health Organization; HIV, human immunodeficiency virus; IPTp, Sulfadoxine-Pyrimethamine for intermittent preventive treatment for malaria during pregnancy; ITN, Insecticide Treated Nets; USD, United States Dollar; GA, gestational age.

Background

Antenatal care (ANC) was a concept created in the early decades of the past century that is now widely acknowledged for its potential for improving newborn survival and health [1–3]. Thus, efforts to tackle low-quality ANC are a key strategy to reduce the high-burden of neonatal morbidity and mortality in sub-Saharan African (SSA) countries [4, 5].

The World Health Organization (WHO) latest recommendations on "antenatal care for a positive pregnancy experience" state that it should start early for timely detection and treatment of maternal problems with a goal of a minimum of eight contacts per pregnant woman [6]. This guideline was published in 2016, and currently, most SSA countries are still in transition from the previous four ANC visits from the 2001 Focused Antenatal Care (FANC) model [2, 7, 8]. In addition, the WHO also preconizes a package of evidence-based screenings for detecting maternal problems and implementing prompt treatments. For instance, interventions such as timely maternal HIV diagnosis can reduce neonatal transmission of HIV to less than 5% with initiation of antiretroviral treatments [9–11]. Additionally, syphilis, when properly treated, prevents small birth weight deliveries in 20% and stillbirths up to 40% [6, 10, 12]. Other ANC screenings are also designed to prevent adverse birth outcomes (ABOs). Anemia in pregnant women, for instance, is another major setback in newborn health, causing different ABOs, such as intrauterine growth retardation, prematurity, low birth weight (LBW), and fetal death [13]. Asymptomatic urinary tract infection in pregnancy, when not treated, is also associated with a 30% risk of developing maternal pyelonephritis, causing ABOs such as LBW and/or preterm delivery [14, 15].

Another example is the prevention of Rh alloimmunization and detection of sickle cell disease (SCD). Alloimmunization prevention reduces perinatal ABOs during a second RhD-positive pregnancy [16]. In its mildest form, the newborn has sensitized red blood cells; on the other hand, the severe form of hemolytic disease may result in intrauterine death or newborn jaundice, anemia, and infant developmental problems [16, 17]. The setback is that antenatal prophylaxis with anti-D immunoglobulin in nonsensitized Rh-negative women at 28 and 34 weeks of gestation is not available in most SSA countries [16]. Similarly, SCD is often undiagnosed in SSA and is associated with complications such as, fetal loss and intrauterine growth restriction [18]. Additionally, the high prevalence of this undiagnosed noncommunicable disease contributes to excess mortality in children under five years of age in Africa [18].

For all the above reasons, ANC is an excellent opportunity to reach pregnant women to prevent neonatal mortality and ABOs, providing a full package with prophylactic medication, vaccines, diagnosis, and treatment, as well as with health education programs [19–23].

Currently, ANC varies tremendously among SSA countries due to factors related to national health policies, screening costs, facilities, and users [24–26]. Additionally, most studies in this field, conducted in SSA contexts, are mainly focused only on the coverage and total number of ANC contacts, disregarding screenings and interventions accomplished [27–29].

Sao Tome & Principe (STP), a SSA Western country, has two islands, with a total land surface of approximately 1,001 km^2 (859 km^2 for Sao Tome and 142 km^2 for Principe) [30–32]. The country has no land borders, but lies relatively close to the coasts of Gabon, Equatorial Guinea, Cameroon, and Nigeria. The country has already reached some of the WHO indicator goals, such as 98% of pregnant women accessing ANC at least once, 95.4% receiving the service of a skilled birth attendant at birth, and 91% obtaining first postnatal care within the first 24 hours after birth [30]. Additionally, there was considerable progress in the country for the maternal mortality ratio, with a reduction from 158 to 74 maternal deaths per 100,000 live births between 2009 and 2014, although neonatal mortality remains a problem [30, 31]. Moreover, ABOs, such as preterm delivery, LBW, small for gestational age, neonatal sepsis, and

congenital anomalies, all amenable to prevention with high-quality ANC, are also a high-burden in STP [22, 32, 33].

In STP, the transition from the model of four ANC visits to the latest WHO recommendation of eight contacts occurred between 2017 and 2018 [32]. Actual ANC free-package in the country includes blood pressure measurement, iron/folic acid supplementation, malaria prevention, tetanus vaccination, and rapid tests (HIV, syphilis, and hepatitis B surface antigen). Blood tests (hemoglobin, glucose, blood group, Rhesus factor, sickle cell, widal test), urine tests, vaginal swabs, coproparasitological exams, and obstetric ultrasounds are requested but have costs for pregnant women [32]. The ANC interventions are documented in an ANC pregnancy card that is carried by all pregnant women to ANC services and to the maternity unit.

Therefore, this study aimed to fill the gaps in ANC—beyond the number of contacts—by identifying screenings performed, maternal problems detected, and treatments provided. To the authors' knowledge, no study on ANC has ever been done in STP. This current study is included in a broader project on neonatal mortality and adverse birth outcomes in Sao Tome & Principe [34–36].

With this study, we intended to contribute to the development of a strategy to improve ANC in STP for neonatal mortality and ABOs high-burden reduction as endorsed in the post-2015 Sustainable Development Goals (target 3.1) [22, 37, 38].

Material and methods

Ethics statement

The study was approved and consented to by the Ministry of Health of Sao Tome & Principe and by the main board of Hospital Dr. Ayres de Menezes, since at the time the study protocol was submitted, there was no ethics committee in Sao Tome & Principe. Only recently has the country National Ethics Committee been appointed. Previously, study analysis and approval were performed by the Ministry of Health and the institution where the study was to be conducted, and that is what we have done. All methods were performed in accordance with the relevant guidelines and regulations in practice. Written informed consent was obtained from all participants (or their parent or legal guardian in the case of adolescent under 16 or illiterate participants) after the purpose of the research to review the information documented in the ANC pregnancy card was explained orally by the main investigator. Participation in the survey was voluntary, as participants could decline to participate at any time during the study.

Study design

This was a retrospective, hospital-based analytical study conducted among pregnant women admitted to the maternity unit of the Hospital Dr. Ayres de Menezes (HAM) for delivery. A total of 511 pregnant women's ANC pregnancy cards were reviewed. This study was purely descriptive in nature as part of the study design.

Setting

The study was conducted at the maternity unit of Hospital Dr. Ayres de Menezes (HAM), the only hospital in the country. This maternity unit is responsible for the delivery of 82.4% of all newborns in STP, representing a 4.500 annual birth cohort [32]. Therefore, this study setting allows to have a global picture of ANC practices in the country.

Antenatal care services in STP are available to women on all working days and contacts are carried out by nurses [32]. They are normally organized along the five thematic components

of service provision stipulated by the WHO guidelines: 1) history taking, 2) physical examination, 3) laboratory examinations, 4) drug administration and immunization and 5) health education [6, 24]. ANC pregnancy cards are an important working tool. In Sao Tome & Principe, it has ten pages, and health workers use them to follow-up the pregnancy by registering personal information, physical examinations, laboratory tests, treatments, and other notes. Pregnant women carry the ANC pregnancy card to each ANC contact and to the hospital at the time of delivery. Screening of human immunodeficiency virus (Determine test), hepatitis B virus (hepatitis B surface antigen—HBsAg) and syphilis (rapid plasma reagin test) are included in the STP´s essential package of interventions for maternal and newborn health, which is done using an opt-out approach and free of charge [23]. Other essential laboratory tests, rapid tests and ultrasounds have costs for pregnant women. Each woman pays approximately 17 United States Dollar (USD) for all mandatory tests (blood, urine, feces, gynecological exams) and obstetric ultrasounds [32].

Midstream urine culture (the gold standard) is the recommended method for diagnosing asymptomatic bacteriuria, but urine culture is not available in STP, so urine dipstick tests in health posts and laboratory urine in other centers are the methods used [6, 32].

Full blood count testing for diagnosing anemia in pregnancy is available only at HAM [8, 13, 32]. Other ANC services perform on-site hemoglobin testing using a hemoglobinometer.

Blood culture is commonly used as the reference standard for typhoid diagnosis but requires sophisticated equipment not readily available in most SSAs, as in STP [39–41]. The Widal test is a quantitative agglutination test that identifies serum antibodies against Salmonella antigens O-somatic and H-flagellar, and in STP, it is performed once during pregnancy [41]. The test is considered positive if a convalescent phase serum sample has a fourfold higher titter than an acute sample [41].

A sickle cell solubility test, which involves treating a thin blood film with sodium dithionate under hypoxic conditions and observing for sickling under a light microscope, is the screening technique available in STP and is performed on pregnant women with anemia or clinical suspicion [42, 43]. A positive result can suggest either sickle cell anemia or the sickle cell trait [42]. The diagnosis of sickle cell disease cannot be established with certainty by means of the sickling test alone but must be substantiated by electrophoretic analysis, unfortunately not available in the country [32].

Participants

All pregnant women admitted to the HAM maternity unit for delivery constituted the source population, whereas the study populations were selected pregnant women admitted to the HAM maternity unit during the study period. The recruitment occurred from July 2016 to November 2018.

The eligibility criteria for participants were as follows: 1) all women admitted to the hospital for delivery with a gestational age of 28 weeks or more and 2) women who gave birth outside the hospital but were later admitted at HAM on the day of birth.

The exclusion criteria included the following: 1) women with induced termination of pregnancy for medical reasons, 2) adolescent or illiterate mothers who had not obtained permission from their parents or legal guardians to participate in the study, and 3) women without an ANC pregnancy card.

Of the 534 eligible participants, 16 women were excluded, nine due to not having an ANC pregnancy card and seven due to missing information on the ANC regarding the number of ANC contacts. A total of five hundred and eleven pregnant women were included in this study.

Sampling method

The software used for sample calculation was Raosoft (http://www.raosoft.com/samplesize.html), and the value sample was also supported by PASS software (https://www.ncss.com/software/pass/). A minimum sample size of S = 355 was recommended, which placed the right dimension between 355 (95%) and 579 (99%) confidence. For the original study, participants were enrolled based on the following assumptions: two-sided 95% confidence level, power of 80% to detect an odds ratio of at least 2 for adverse birth outcomes. Since the sample size was not calculated for present outcomes, a power analysis was performed, varying from 77% to 87% for outcomes such as having four ANC contacts for this study.

Pregnant women were invited to participate in the study after admission to the maternity unit. Invitations were made by the investigator (AV) and occurred during daytime hours, from Monday to Friday. Participants were selected randomly until the required sample size was achieved. Each morning, from the pile of pregnant women admission folders, every second interval folder was selected and then carried on asking for consent for enrollment before starting the data collection.

Data sources

The ANC pregnancy card of each study participant was used to collect personal data, obstetric and pregnancy information as well as physical examinations, laboratory tests, and treatments.

Study variables

The information was collected from ANC pregnancy cards on mothers' age, place of residence, educational status, occupation, and obstetrics characteristics such as: parity, gravidity, history of abortion and stillbirth. Gravidity was categorized as primigravida (1), multigravida (2–4) and grandmultigravida (above 5). Parity was classified as nulliparous (0), multiparous (1–4) and grandmultigravida (above 5).

Employment was defined for those who engaged in one economic activity and not employed for those who did not engage in economic activities. Residence was grouped into urban and rural areas. The urban area was living in the Água Grande district and rural areas in Mé-Zochi, Cantagalo, Lobata, Lembá, Caué and Principe Island.

For ANC characterization, the following variables were included: timing at first ANC booking on the first (conception to 13th gestational age week), second (14–26 week) or third trimester (27–40 week), number of ANC contacts, high-risk pregnancy scoring notification, screenings, interventions, diagnosis, and treatments. Reasons registered by the nurses in the ANC pregnancy cards justifying why the screenings were not performed were also collected. The main evidence-based interventions were grouped, described, and compared according to the number of ANC contacts per pregnant woman: 1–3 (inadequate), 4 to 7 visits (adequate) and 8 or more (complete) [22–25].

Bias

As this was a retrospective study, the reasons for the poorly recorded information were not explored, and only the completeness of the recording could be analyzed.

Data management and quality

Data were secured in a confidential and private location. Participants were referred to by identification numbers, and the informed consent forms were kept separate. Both could only be linked by a coding sheet available to the investigator. Supervision of data collection and

continuous follow-up were made by the supervisors. The investigator (a pediatrician) executed and was responsible for field study activities as follows: obtaining consent and enrollment of the pregnant women, data collection from ANC pregnancy cards, and entry into the database.

Statistical methods

ANC characterization (screenings, diagnosis, and treatments) and characteristics of study participants were described with frequencies and percentages or mean (standard deviation) and range (min-max), as appropriate. Comparisons of screenings between the different groups (inadequate ANC, adequate and complete ANC) were assessed using the Chi-squared test or Fisher's exact test. A level of significance $\alpha = 0.05$ was considered. Data collected from the ANC pregnancy card were directly entered into QuickTapSurvey (2010–2021 Formstack) an offline survey app tool, and further analysis was conducted in the Statistical Package for the Social Sciences for Windows, version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Sociodemographic characteristics of the study participants

A total of 511 pregnant women´s ANC pregnancy cards were reviewed. The mother´s mean age was 26.6 (7.1) years old, between 14 and 43 years of age. Twenty-eight (5.5%) were aged between 14 and 16, 14.7% (75) 17–19, 63.2% (323) 20–34 years and 16.6% (85) were older than 35 years of age. Regarding mothers´ education, 57.9% (296) had primary education, and 32.1% (164) had secondary education. Higher education was found in 6.5% (33). Illiteracy was found in 3.5% (18). Concerning employment status, 70.6% (361) were not employed, and 28.8% (147) were employed. Urban area living was confirmed in 44.6% (228), while 53.6% (274) were living in rural areas, such as Mé-Zochi 28.4% (146), Cantagalo 11.4% (58), Lobata 6.3% (32), Lembá 4.3% (22), Caué 1.8% (9) and Principe Island 1.4% (7).

Antenatal care (ANC) characterization

ANC: Timing and number of contacts. Early first ANC contact during the first trimester of gestation was reached by 51.7% (268/446) of pregnant women. Late booking with a first ANC contact during the second and third trimesters occurred in 31.5% (163/446) and 2.9% (15/446) of participants, respectively. Data regarding the timing of the first ANC attendance were missing from 65 (14.6%) ANC pregnancy cards. The detailed distribution of gestational age in weeks and by trimester at the initiation of ANC contact is shown in Fig 1. Regarding the total number of ANC contacts, 14.9% (76) had fewer than 4 ANC contacts, 46.4% (237) had 4 to 7 and 38.7% (198) had complete ANC ($\geq$8 contacts) as described in Table 1.

ANC: High-risk pregnancy scoring. Notification of a high-risk pregnancy was registered in 31.5% (161) of cases. Maternal age as a risk factor was recorded in 22.5% (115) of ANC cards: adolescent pregnancy ($\leq$16 years old) in 5.5% (28) and 17% (87) higher than 35 years old. Thirty percent (155) had a prior history of miscarriages, and 3.9% (20) had stillbirths, although no more details were specified in their ANC cards. A rate of 10% was found for grandmultiparous women.

ANC: Screenings, maternal diagnosis, and treatments. Table 1 describes the screenings registered in the ANC pregnancy cards for the study participants (n = 511) and according to the number of ANC contacts: inadequate (1–3), adequate (4–7) and complete (8 and above). Lack of economic support in 36% (184) and lack of reagents in 2% (10) were the reasons registered in the ANC pregnancy cards for screening absence. Pregnant women had no screening

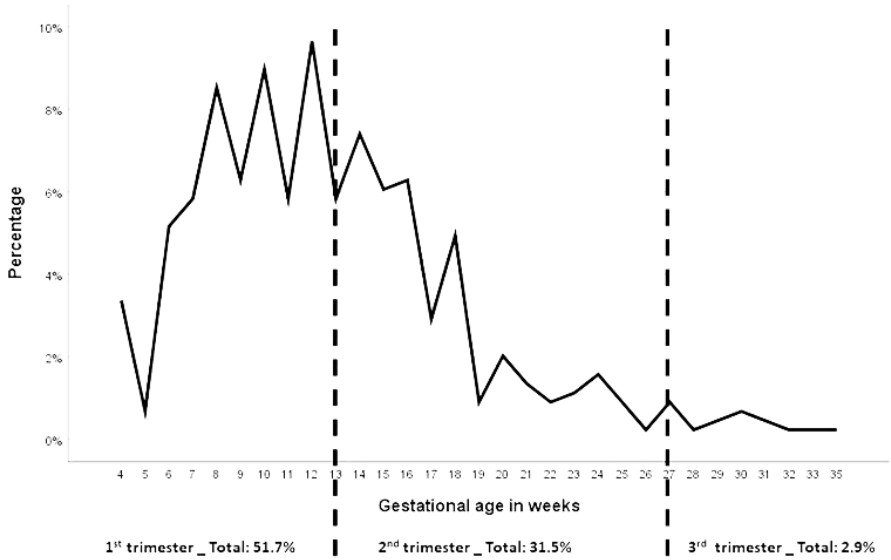


Fig 1. Timing of first ANC contact according to gestational age in weeks and trimesters (data for 446 participants). Distribution of gestational age in weeks and by trimester at the initiation of ANC contact, as follow: 51.7% (268/446) in the first trimester, 31.5% (163/446) during the second and 2.9% (15/446) in the third trimester. Data regarding the timing of the first ANC contact were missing from 65 (14.6%) ANC pregnancy cards.

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done for HIV in 4.5%, syphilis in 8.8%, HBV 39.3%, malaria 25.8%, hemoglobin 24.5%, urine test 29.7%, blood glucose in 45.4%, stool exams 27.8% and 41.1% had no ultrasound.

Screening completion for blood group, HIV, malaria, urine, hemoglobin, and coproparasitological exam were found to have a statistically significant difference ($p<0.001$) for the complete ANC group when compared to the inadequate and adequate ANC groups as described in Table 1.

Free interventions, such as administration of one dose of sulfadoxine-pyrimethamine for intermittent preventive treatment for malaria during pregnancy (IPTp), were given to 47.4% (242) of women, 43% (220) received the two doses, and 9.6% (49) had none. Insecticide-treated nets were delivered to 88.5% (442) of the pregnant women. Regarding immunization, 94.5% (483) had received tetanus toxoid immunization as follows: 1.8% (9) had one dose, 30.5% (155) had two, 22.3% (114) had three, 17% (87) had four, and 23% (118) had the complete five doses. No dose was registered in 5.5% (28) of the ANC pregnancy cards.

The identified maternal ANC diagnosis and treatments prescribed are described in Table 2. Additional maternal problems identified during ANC follow-up were first-trimester bleeding in 0.2% (1), second trimester bleeding in 0.2% (1), and third trimester bleeding in 1.2% (6). All pregnant women with preeclampsia and bleeding were referred to the HAM maternity unit for further evaluation.

Discussion

Neonatal mortality rate and morbidity due to adverse birth outcomes (ABOs) in Sao Tome & Principe remain high despite the recent significant reduction in maternal deaths [30–32]. Thus, we sought to analyze ANC through screenings performed and problems commonly detected among pregnant women in STP, since a key component to reduce neonatal morbidity and mortality is having a high-quality ANC [1–3].

Table 1. Screening completion comparison according to the frequency of ANC contacts: Inadequate (1 to 3), adequate (4 to 7) and complete (≥8).

	Total n = 511 (%)	1–3 ANC contacts n = 76 (14.9%)	4 to 7 ANC contacts n = 237 (46.4%)	≥8 ANC contacts n = 198 (38.7%)	p-value
Blood group					
yes	333 (65.2)	24 (31.6)	152 (64.1)	157 (79.3)	<0.001#
no	178 (34.8)	52 (68.4)	85 (35.9)	41 (20.7)	
HIV					
tested once	213 (41.7)	52 (68.4)	104 (43.9)	57 (28.8)	<0.001#
tested twice	275 (53.8)	20 (26.3)	126 (53.2)	129 (65.2)	
not tested	23 (4.5)	4 (5.3)	7 (2.9)	12 (6.0)	
Syphilis					
tested once	460 (90.0)	69 (90.8)	212 (89.5)	179 (90.4)	0.717*
tested twice	6 (1.2)	0	2 (0.8)	4 (2.0)	
not tested	45 (8.8)	7 (9.2)	23 (9.7)	15 (7.6)	
Hepatitis B					
tested	310 (60.7)	47 (61.8)	143 (60.3)	120 (60.6)	0.870*
not tested	201 (39.3)	29 (38.2)	94 (39.7)	78 (39.4)	
Malaria					
tested once	342 (66.9)	24 (31.6)	163 (68.8)	155 (78.3)	<0.001#
tested twice	37 (7.2)	1 (1.3)	14 (5.9)	22 (11.1)	
not tested	132 (25.8)	51 (67.1)	60 (25.3)	21 (10.6)	
Urine					
tested once	296 (58)	27 (35.5)	150 (63.3)	119 (60.1)	<0.001#
tested twice	63 (12.3)	0	17 (7.2)	46 (23.2)	
not tested	152 (29.7)	49 (64.5)	70 (29.5)	33 (16.7)	
Coproparasitological exam					
tested once	329 (64.4)	24 (31.6)	164 (69.2)	141 (71.2)	<0.001#
tested twice	40 (7.8)	0	8 (3.4)	32 (16.2)	
not tested	142 (27.8)	52 (68.4)	65 (27.4)	25 (12.6)	
Hemoglobin test					
tested once	296 (57.9)	24 (31.6)	158 (66.7)	114 (57.6)	<0.001#
tested twice	90 (17.6)	2 (2.6)	25 (10.5)	63 (31.8)	
not tested	125 (24.5)	50 (65.8)	54 (22.8)	21 (10.6)	
Ultrasound					
0	210 (41.1)	60 (78.9)	93 (39.2)	57 (28.8)	<0.001#
1	216 (42.3)	13 (17.1)	114 (48.2)	89 (44.9)	
2	72 (14.1)	2 (2.6)	23 (9.7)	47 (23.7)	
≥3	13 (2.5)	1 (1.3)	7 (2.9)	5 (2.5)	
First trimester ultrasound	161/216 (74.5)	6/13 (46.1)	66/114 (57.9)	89/89 (100)	0.005#

#Pearson Chi-Square

*Fisher´s Exact Test

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Antenatal care coverage in Sao Tome & Príncipe is a success compared to other SSA countries [8, 44]. Attendances are extremely high for a low-resource country. The minimum of eight ANC contacts, endorsed by the 2016 WHO´s guideline, was reached in almost forty percent. Moreover, 85.1% of the participants had four or more contacts when the rates reported in SSA for 4 visits were approximately 62% [44]. Regarding the timing of the first ANC booking, we also found a high percentage of pregnant women with early contact during the first

Table 2. Total screenings performed, maternal ANC diagnosis and treatments prescribed for study participants (511).

ANC screenings	Total performed (at least once) (%)	Positive results/maternal ANC diagnosis (%)	Treatment administration (%)
HIV[†]	488 (95.4)	4 (0.8)	4 (100) received antiretroviral
Syphilis[†]	466 (91.2)	5 (1.0)	3 (60) received ANC penicillin
Hepatitis B virus (HBV) surface antigen[†]	310 (60.7)	18 (5.8)	6 (33.3) newborns received selective hepatitis B birth-dose vaccination (HepB-BD)[1]
Malaria[†]	379 (74.2)	3 (0.8)	3 received artemisinin-based combination therapy
Blood group test*	334 (65.3)	-	-
Rhesus factor for Rh negative**	326 (63.8)	19 (5.8)	No
Hemoglobin for anemia***	386 (75.6)	143 (37)	No
Blood glucose for hyperglicemia****	279 (54.6)	10 (3.6)	No
Urine for bacteriuria	359 (70.2)	155 (43.2)	97 (62.5) received antibiotic: amoxicillin 92.7% (90/97) ampicillin 5.5% (5/97) cefotaxime 2% (2/97)
Coproparasitological exam for pathogenic intestinal parasite	369 (72.2)	220 (59.2)	55 (25)
Vaginal smear for candida infection	351 (68.7)	104 (29.6)	104 (100) treated with nitroimidazoles
Widal test for typhoid fever	236 (46.2)	35 (14.8)	35 (100) were treated with amoxicillin
Sickling rapid laboratory test for sickle cell disease or trait	284 (55.6)	37 (13)	No
Blood pressure measurement[†]	414 (81)	37 (7.1) preeclampsia	37 (100)
Obstetric ultrasound	301 (58.9)	15 twin pregnancies 2 major fetal malformations	-

[†]free of costs screening tests

[1]While this study was being conducted, there was an expansion to universal newborn hepatitis B birth-dose vaccination (HepB-BD) without maternal screening. Before that, the country had a selective hepatitis B birth-dose vaccination (HepB-BD) strategy targeting infants born to mothers who tested positive for hepatitis B virus (HBV) surface antigen.

*17.4% (58) were group A, 26.3% (88) group B, 54.8% (183) group 0, and 1.5% (5) were group AB

**anti-D immunoglobulin is not available in STP

***Anemia was defined as a hemoglobin value less than 11 g/dL. ANC supplementation with iron/folate tablets was prescribed to 86.8% (444) of pregnant women, and no additional measure was described in the ANC pregnancy card for anemic mothers.

****Hyperglycemia was defined as glucose ≥105 mg/dL. No special measure or treatment was registered in these pregnant women ANC cards.

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trimester. This finding of 51.7% is much higher than other studies in SSA, per example, Tanzania with 12.4%, Nigeria with 15.4%, Zambia with 17%, and Ethiopia with 27.5% [24, 45–47].

However, this is not equivalent to the provision of good quality ANC since most pregnant women in this study missed screenings, diagnosis, and treatments, which has an impact on neonatal health outcomes, highlighting an important ANC coverage-quality gap in Sao Tome & Principe [33]. For instance, anemia during pregnancy is a public health problem that leads to different life-threatening complications and poor pregnancy outcomes [13]. In this study, among those who were tested, 37% were anemic, similar to the 41.8% overall prevalence of maternal anemia in Africa [13]. Thus, anemia during pregnancy should be urgently addressed in STP to prevent related complications such as intrauterine growth retardation, prematurity, LBW, and fetal death [13].

Another maternal issue related to ABOs identified in this study is the high prevalence of asymptomatic urinary tract infections in pregnancy. From those who were able to perform a urine test, we identified a rate of 43.2% bacteriuria, which is more than double the range usually reported for pregnant women in SSA (2% to 16.43%) [14, 15, 47]. In addition to the high

prevalence of bacteriuria, we also identified that almost half of those in this situation go through all pregnancy without either receiving antibiotic treatment or repeating the urine test. Furthermore, and unlike culture (not available at STP), urinalysis fails to identify the etiologic agents and the antibiotic sensitivity pattern. Due to the above reasons, the real burden of bacteriuria in pregnant women and its associated neonatal complications (LBW and/or preterm birth) in STP are highly underestimated and need specific measures to address it.

Intestinal parasitic infections are known to be extremely frequent among children in STP [48], and in this study, we were able to identify that sixty percent of the pregnant women enrolled had at least one pathogenic intestinal parasite infection documented in their ANC pregnancy card. Anthelmintic treatment was administered in approximately one-quarter of pregnant women. Thus, considering this high prevalence as well as the burden of maternal anemia in the country, the implementation of preventive anthelminthic treatment for pregnant women after the first trimester as part of worm infection reduction programs should be discussed [6, 32].

Malaria was detected in three (0.8%) pregnant women, while prophylaxis with intermittent preventive treatment for malaria during pregnancy was provided to half of the women and a high proportion received an insecticide-treated net, similar to other nearby countries, such as Gabon [49].

HIV was detected in less than one percent of pregnant women, which is in accordance with published data (0.2%) for the country [49]. Syphilis was diagnosed in 1%, lower than the estimated pooled prevalence of syphilis of 2.87% for SSA [12]. This is a noteworthy point in the context of the triple elimination of HIV, syphilis and hepatitis B in Sao Tome & Principe [50–52].

Typhoid fever is endemic in STP, as it is common in SSA, which lacks access to clean water and adequate sanitation and found on 14.8% of pregnant women [40, 41]. However, the efficiency of the Widal test in diagnosing typhoid fever without other confirmatory tests is not of diagnostic value; thus, it should not be performed as a routine antenatal care practice in STP [53].

The low rate of gestational diabetes mellitus in this study can also be underestimating the reality, taking into consideration that half of the pregnant women only tested once for blood glucose. The number of preeclampsia cases detected was 7%, which is in accordance with the range of 3% to 10% published for SSA countries [54]. Another concern identified in this study is the risk for RhD alloimmunization, as the Rhesus factor was negative in 5.8% of pregnant women, similar to other nearby countries [16].

Sickle cell disease (SCD) or trait was suspected in 13% of pregnant women, highlighting a crucial need to understand the real burden of SCD in the country.

Regarding evidence-based screenings performed according to the number of ANC contacts, pregnant women with complete ANC had more screening completion in comparison to those with adequate and inadequate ANC, with a statistically significant difference ($p<0.001$). Nonetheless, having two hemoglobin and urine tests was only accomplished by thirty percent of those with complete ANC ($\geq$8 contacts), illustrating that most pregnant women, even those with complete ANC, are not able to accomplish the minimum recommended screenings throughout the pregnancy.

It should be highlighted that all the above discussed antenatal diagnoses are underestimated since many pregnant women in this study did not test at all, and lack of economic support was the main reason documented. Pregnant women may not have the financial resources needed to pay for ANC screenings, especially if they cost 17 USD when living on a budget of 1.40 USD per day [32]. Missing out these evidence-based ANC screenings and interventions due to their high-costs represents losing the momentum for adequate antepartum intervention of maternal

conditions amenable to treatment, consequently missing key opportunities in the prevention of risk factors linked to perinatal mortality and ABOs [5, 6, 22]. Therefore, providing a health system in STP that broadens the benefits of free ANC screening can go a long way to improve long-term gains for maternal and newborn health [22, 24, 37, 47].

Strengths and limitations

This study has the strength of being based on a large national sample. We included data from ANC pregnancy cards from 511 pregnant women, a similar sample used in the 2019 Multiple Indicator Cluster Survey (MICS) for Sao Tome & Principe from UNICEF [30]. Moreover, contrary to MICS, our study is not vulnerable to recall bias, as the mothers included had the ANC card with them and had just delivered the baby. Additionally, most of the studies in SSA only analyze ANC utilization in terms of the number and timing of attendances. Our study included routine screenings, maternal diagnosis, and treatments in addition to the number of contacts per pregnant woman. Moreover, this study was conducted on HAM, where approximately 82% of all births in the country take place; therefore, it also covered most rural areas.

Therefore, this study can be a model for other similar low-resource countries for detecting the main gaps in the country´s ANC service, enabling the design of target intervention and better allocation of resources to where they are needed.

However, there were some limitations that should be pointed out: proper records and quality of care given could not be assessed, and ANC practices may differ in terms of access to health care, health worker motivation and training, and availability of health service across the islands. The STP´s ANC pregnancy card was designed to make documentation complete and easier, but it was found that important information was not always adequately recorded by the nurses. Details of previous pregnancies, contraception, planned pregnancy, present medical problems and signaling of high-risk pregnancies were often missing. Height, weight, and body mass index are not registered during ANC visits in STP, as it is not mandatory according to the WHO 2016 recommendations, but this could be reviewed for this setting [6].

Conclusion

Sao Tome & Principe have made remarkable progress toward ensuring that no pregnant woman is left without antenatal care. Nonetheless, most still miss evidence-based screenings, diagnosis, and treatment opportunities with an impact on neonatal health outcomes.

Strategies such as 1) screening all pregnant women for anemia and bacteriuria, 2) preventive administration of anthelmintic drugs after the first trimester, 3) implementation of universal access to anti-D immunoglobulin for Rh-negative pregnant women, 4) provision of novel inexpensive sickle cell disease point-of-care test kits in the country, and 5) implementation of a total free antenatal care health policy should be discussed due to the country profile and for enhancing neonatal health outcomes.

These measures would enhance the prompt detection of maternal problems amenable to ANC treatment, preventing ABOs and reducing neonatal mortality in STP.

Supporting information

S1 Text. Inclusivity in global research.
(DOCX)

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Determinants of antenatal care utilization – contacts and screenings – in Sao Tome & Principe: a hospital-based cross-sectional study

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Abstract

Background Sao Tome & Principe (STP) has a high peri-neonatal mortality rate and access to high-quality care before childbirth has been described as one of the most effective means of reducing it. The country has a gap in the coverage-content of antenatal care (ANC) services that must be addressed to better allocate resources to ultimately improve maternal and neonatal health. Therefore, this study aimed to identify the determinants for adequate ANC utilization considering the number and timing of ANC contacts and screening completion.

Methods A hospital based cross-sectional study was undertaken among women admitted for delivery at Hospital Dr. Ayres de Menezes (HAM). Data were abstracted from ANC pregnancy cards and from a structured face-to-face interviewer-administered questionnaire. ANC utilization was classified as partial vs adequate. Adequate ANC utilization was defined as having ANC 4 or more contacts, first trimester enrolment plus one or more hemoglobin tests, urine, and ultrasound. The collected data were entered into QuickTapSurvey and exported to SPSS version 25 for analysis. Multivariable logistic regression was used to identify determinants of adequate ANC utilization at *P*-value < 0.05.

Results A total of 445 mothers were included with a mean age of 26.6 ± 7.1, an adequate ANC utilization was identified in 213 (47.9%; 95% CI: 43.3–52.5) and a partial ANC utilization in 232 (52.1%; 95% CI: 47.5–56.7). Age 20–34 [AOR 2.27 (95% CI: 1.28–4.04), $p = 0.005$] and age above 35 [AOR 2.5 (95% CI: 1.21–5.20), $p = 0.013$] when comparing with women aged 14–19 years, urban residence [AOR 1.98 (95% CI: 1.28–3.06), $p < 0.002$], and planned pregnancy [AOR 2.67 (95% CI: 1.6–4.2), $p < 0.001$] were the determinants of adequate ANC utilization.

Conclusion Less than half of the pregnant women had adequate ANC utilization. Maternal age, residence and type of pregnancy planning were the determinants for adequate ANC utilization. Stakeholders should focus on raising awareness of the importance of ANC screening and engaging more vulnerable women in earlier utilization of family planning services and choosing a pregnancy plan, as a key strategy to improve neonatal health outcomes in STP.

Keywords Antenatal care utilization, Sao Tome & Príncipe, Pregnant women, Newborn mortality, Antenatal screenings, Adequate antenatal care utilization

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Text box 1. Contributions to the literature

- Achieving a 90% coverage rate of 4+ ANC contacts by 2025 is one of the targets of the 90/90/80/80 milestones. Low-resource settings, such as Sao Tome & Principe, are far behind with major gaps in the quality of ANC coverage-content.
- Missing out ANC screenings represents losing the prevention and treatment of adverse outcomes, such as low-birthweight, prematurity, sepsis, and stillbirths.
- This study adds to the literature as it addresses the determinants of ANC utilization, classified as adequate or partial based on the number of ANC contacts, timing of first booking plus the completion of hemoglobin, urine tests and obstetric ultrasound.

Background

Poor antenatal healthcare (ANC) utilization is an international public health challenge especially in low-resource countries, with prejudice toward the health of the expectant mother and the unborn child [1, 2]. Access to a quality ANC service remains a major challenge in efforts to reduce neonatal morbidity and mortality [1].

Antenatal care status is typically characterized only by the number or timing of visits or ANC contacts [3]. However, these optimum numbers of attendances have been changing in recent decades. Initially, the World Health Organization (WHO) suggested numerous ANC visits (7–16), a burden in resource-constrained settings; then, in 2001, Focused Antenatal Care (FANC) reduced it to a minimum of four visits [4, 5]. Later, studies concluded that eight ANC contacts could reduce perinatal deaths by up to eight per 1000 births when compared to four visits [6]. Consequently, in 2016, the WHO established eight ANC contacts to reduce perinatal mortality and improve mothers' experience of care [7].

Evidence-based screenings are also endorsed by the WHO, including a core set of interventions such as blood pressure measurement, iron tablet supplementation, tetanus toxoid vaccination, urine testing, hemoglobin test, and rapid tests for sexually transmitted diseases [1]. These screenings are able to identify unrecognized diseases or conditions in apparently healthy pregnant women by means of tests that can be applied rapidly and easily to the target population with irrefutable benefits in maternal and neonatal health [1, 8].

Nonetheless, there is a gap in the actual use and implementation of these ANC screening practices, mainly in sub-Saharan African (SSA) countries [8].

The magnitude of the gap varies, with greater concerns reported in relation to underuse compared to overuse, mainly in screening completion [8].

Factors linked to maternal ANC utilization, are usually grouped into community-level features, sociodemographic and pregnancy-related characteristics, media exposure and availability of maternal health services [2]. Effectively, the determinants of ANC utilization are maternal education, women's employment, marital status, husband's education, household income, availability, cost, and pregnant women's history of obstetric complications [8, 1]. These factors can influence the ANC use of these women either positively or negatively [1].

Sao Tome & Principe (STP), a sub-Sharan Island country in the Gulf of Guinea, is characterized by a total fertility rate of 4.4 (number of births per woman) and a considerable unmet need for contraception of 33.7% [9]. Although ANC contacts are available free of charge to all women, most screenings have high costs to pregnant women, limiting their completion and the quality of care provided [9].

The country already reached two out of four 90/90/80/80 targets and milestones for maternal and newborn health, with 95.4% women receiving the service of a skilled birth attendant at birth and 91% newborns obtaining first postnatal care within the first 24 h after birth [9, 10]. Missing the target of 90% coverage of ANC 4 or more contacts and the 80% availability at the districts of critical emergency care for women with complications and for small and sick newborns [9, 10]. Despite all these achievements, at the start of this research, neonatal mortality in STP was high, with 22 newborn babies dying per 1000 live births and 22 stillbirths per 1000 live births [11].

Most studies about ANC in Sub-Saharan countries dichotomize the outcome variable ANC into utilized and not utilized—only based on the total number of visits/contacts—disregarding whether the WHO´s recommended screenings were completed [12, 13]. Missing out on these evidence-based screening interventions represents losing the prevention or treatment of maternal anemia, bacteriuria, puerperal sepsis, reduction of the risk of low-birth-weight neonates, preterm birth, neonatal sepsis, and stillbirths [7, 12, 13]. ANC optimization has a key role in reducing of neonatal mortality and adverse birth outcomes and improving overall neonatal health outcomes [2]. Therefore, in the present study, we decided to go further on and assess essential ANC screening per pregnant woman (obstetric ultrasound, hemoglobin, and urine tests), in addition to the total number of ANC contacts [14]. We now aim to understand pregnant women´s profile depending on the type of ANC utilization with the purpose of contributing to the development of a strategy to improve maternal and newborn health as endorsed in the post-2015 Sustainable Development Goals of no more than 12 neonatal deaths per 1000 livebirths for Sao Tome and Príncipe [15].

Material and methods

Study design and period

An institutional-based cross-sectional analytical study was conducted from July 2016 to November 2018 in the only country´s hospital, Hospital Dr. Ayres de Menezes (HAM).

Study context

The archipelago of STP has two islands, with a total land surface of approximately 1,001 km^2, 859 km^2 of which for Sao Tome and 142 km^2 for Principe with approximately 200.000 inhabitants [9, 10]. All six districts have maternity units: Lembá, Lobata, Caué, Me-Zochi, Principe, Água Grande (HAM), exception for the district of Cantagalo [9, 10]. Complete obstetric services (cesarean section and blood transfusion) are only available at HAM. There is no health insurance policy in the country or any private maternity units. ANC contacts are provided by nurses [7, 9, 16]. The ANC services offered are documented on women´s antenatal pregnancy card, which remains with the pregnant women for taking it to the maternity unit at the time of the babies` delivery.

Study population

This study was conducted in HAM which has a maternity unit responsible for 82,4% of all deliveries in the country [9, 10]. An estimated total number of 4500 births was registered during the study period.

All pregnant women admitted to the HAM maternity unit for delivery constituted the source population, whereas the study populations were selected pregnant women admitted to the HAM maternity unit during the study period.

The eligibility criteria for participants were as follows: 1) all women admitted to the hospital for delivery with a gestational age of 28 weeks or more, 2) prepartum adolescents and illiterate women who had obtained permission from their parent(s) or legal guardian(s) to participate in the study and 3) those who gave birth outside the hospital but were later admitted at HAM on the day of birth.

The exclusion criteria included the following: 1) women with induced termination of pregnancy for medical reasons, 2) adolescent or illiterate mothers who had not obtained permission from their parents or legal guardians to participate in the study, 3) women without an ANC pregnancy card and 4) those missing information on the timing of first ANC contact.

Of the 534 eligible participants, 89 women were excluded (16 for being discharged before conducting the face-to-face interview, 7 due to not having an ANC pregnancy card and 66 due to missing information on the timing of first ANC contact). A total of 445 pregnant women were included in this study.

Sample size determination and sampling procedure

The sample size was calculated using Raosoft software (http://www.raosoft.com/samplesize.html). Using a minimum sample of 10% of the population, validated by the software, placed the sample right dimension between 355 (95%) and 579 (99%) confidence. This size was also supported by PASS software (https://www.ncss.com/software/pass/). It was possible to collect 445 women, which gave some comfort at this level. Eligible cases were selected randomly until the required sample size was achieved.

Data collection tools/methods

Data on this study were gathered through a structured face-to-face interviewer-administered questionnaire plus data abstraction from the pregnant women´s ANC pregnancy card. A structured questionnaire adapted from other similar studies was used [1, 8, 17, 18]. Issues covered in each questionnaire included data on age, residence, maternal education, partner education, maternal occupational status, marriage, planned pregnancy, and previous contraceptive utilization. Some questions had dichotomous answers, for example, type of pregnancy planning (planned or unplanned) and contraceptive use (previous use or never use). In addition to the interview, the researcher abstracted clinical data by reviewing the mother´s ANC pregnancy card to collect information regarding screening tests performed, parity, number of ANC contacts, and timing of first booking.

Data quality control

The questionnaires were administered in Portuguese, the national language in Sao Tome & Principe. Five percent of the questionnaire was pretested in the same study area one month before data collection, and modification was made based on the pretest result. Administered questionnaires were checked for completeness and consistency. Supervision of data collection and continuous follow-up were provided by the supervisors. The main investigator (a pediatrician, PhD researcher) executed and was responsible for all activities as follows: obtaining consent and enrollment of the mothers, data collection from ANC pregnancy cards, face-to-face interviews, and performing all data collection entry into the survey app.

Variables

Outcome variable

The outcome variable of interest was the utilization of ANC services. This utilization was classified as adequate or partial, based on the number of ANC contacts and

first booking in the first trimester as well as the completion of hemoglobin, urine tests and obstetric ultrasound.

Adequate ANC utilization was defined when **all** the following interventions were achieved: 1) attended ANC four or more times, 2) first booking during the first trimester, 3) had at least done one ultrasound, 4) had at least one urine test and 5) performed no less than one hemoglobin test.

Partial ANC utilization category involved the remaining pregnant women, namely, those who attended antenatal clinic one or more times regardless of, whether they had or not, an obstetric ultrasound, an urine or any hemoglobin tests.

Explanatory variables

In accordance with previous knowledge, the variables included in this study that could potentially be associated with ANC service utilization were age, residence, maternal education, husband/partner education, maternal occupational status, marriage, planned pregnancy, contraceptive utilization, and parity [13, 14, 19].

Age was categorized as 14–19 years, 20–34 years and 35 years and above. Women's education level has been included as a categorical variable ranging from no education, primary education, secondary and higher education, the same criteria for the baby's father's education. Household characteristics were characterized as having sanitation (toilet facilities or latrine) or not. Residence was grouped into urban and rural. Urban residence for women living at the capital city (Água Grande) and rural residence in all other districts. Employment status (working or not working) was defined as working for those who engaged in one economic activity. Parity was categorized as nulliparous, one to four parity and grand multipara (five or more). Marital status considered the two categories married/union vs single/never married. Women who were formally married or those who reported being in a union (cohabiting with a partner) were categorized as married/union.

Data management and statistical analysis

Data entry for this study into the app survey was first cleaned by creating a data entry field in Excel, and all categorical responses were checked for completeness and accuracy and to eliminate errors and inconsistent data. Data were further analyzed using the Statistical Package for the Social Sciences for Windows, version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Data analysis in this study was carried out in two stages. The first stage involved pooling data for descriptive statistics with categorical variables presented as frequencies and percentages, and quantitative variables presented as the mean and standard deviation. The second stage involved a univariable analysis to identify the candidate variables for the multivariable analysis (with a p value < 0.25). In all these analyses, logistic regression models for binary response were applied. Linearity in the logit assumption of age was verified with generalized additive regression models. The crude odds ratios (COR) and adjusted odds ratios (AOR) with corresponding 95% confidence intervals (95% CI) were then estimated. The level of significance $\alpha = 0.05$ was considered. The goodness-of-fit of the multivariable model was checked with the Hosmer–Lemeshow test.

Ethics approval and consent to participate

The study was approved and consented to by the Ministry of Health of Sao Tome and Principe and by the main board of Hospital Dr. Ayres de Menezes, since at the time the study protocol was submitted there were no ethics committees in Sao Tome and Principe. Only recently has the country National Ethics Committee been appointed. Previously, study analysis and approval were done by the Ministry of Health and the institution where the study was to be performed, which is what we have done. All methods were performed in accordance with the relevant guidelines and regulations in practice. Written informed consent was obtained from all participants (or their parent or legal guardian in the case of adolescents under 16) after the purpose of the research was explained orally by the main investigator. Additionally, if the mother was illiterate and unable to write, oral consent was given in the presence of at least one witness, usually the ward nurse´s complementarity to the mother´s fingerprint mark in the consent form. Participation in the survey was voluntary, as participants could decline to participate at any time during the study. The anonymity and safety of participants were ensured.

Results

Sociodemographic characteristics of the study participants

Table 1 shows the sociodemographic characteristics of the participants. Of the 445 pregnant women included, 278 (62.5%) were aged 20 to 34, and the mean age was 26.6 ± 7.1 years (minimum age 14 and maximum 43 years). Three hundred seventy (84.9%) participants were married, 250 (56.6%) ended school with a primary level of education, 239 (54.2%) lived in a house with sanitation, and 307 (69.5%) were unemployed.

Pregnancy-related characteristics

A parity of one to four was observed in 271 (60.9%) pregnant women, with 136 (30.6%) of the participants being nulliparous. Unplanned pregnancy was reported in 252

Table 1 Sociodemographic, community-level and pregnancy-related characteristics for pregnant women (445) admitted to Hospital Dr Ayres de Menezes, Sao Tome & Principe (2016–2018)

Variables	Category	Frequency	Percentage
Age	14–19	92	20.7
	20–34	278	62.5
	35 +	75	16.9
Education	none	14	3.1
	primary	250	56.2
	secondary	148	33.3
	higher	33	7.4
Employment	not working	307	69.5
	working	135	30.5
Marital status	union/married	370	84.9
	single	66	15.1
Father education	none	10	3.3
	primary	146	47.9
	secondary	114	37.4
	higher	35	11.5
Residence	urban	202	46.2
	rural	235	53.8
Household sanitation	open defecation	202	45.8
	sanitation	239	54.2
Parity	0	136	30.6
	1–4	271	60.9
	5 +	38	8.5
Pregnancy planning	unplanned	252	68.9
	planned	114	31.1
Contraceptive previous use	yes	90	24.5
	no	278	75.5

(68.9%) cases, and previous contraceptive use occurred in 90 (24.5%) of the participants.

Community-level features

Residency in an urban area was assessed for 202 (46.2%) participants, and 235 (53.8%) were living in rural districts, namely, 129 (30%) in Mé-Zochi, 48 (10.8%) in Cantagalo, 25 (5.6%) in Lobata, 17 (3.8%) in Lembá, 9 (2%) in Caué and 7 (1.6%) in Principe Island.

Antenatal care utilization: adequate versus partial

Of the 445 participants, 378 (84.9%) had four or more ANC visits, 268 (60%) had a first booking during the first trimester, 214 (48%) pregnant women had at least one obstetric ultrasound, 280 (62.9%) had one urine test and 294 (66%) had a hemoglobin test.

The results in Table 2 show the criteria for ANC service utilization classification (adequate versus partial).

Adequate ANC service utilization was identified for 213 (47.9%; 95% CI: 43.3–52.5) pregnant women. Partial ANC service utilization was defined for the remaining 232 (52.1%; 95% CI: 47.5–56.7) women.

Table 2 ANC service utilization among pregnant women enrolled (445)

Variables	Category	Frequency	Percentage
ANC 4 or more contacts	yes	378[a]	84.90%
	no	67	15.10%
Early booking in the 1st trimester	yes	268[a]	60%
	no	177	40%
Obstetric ultrasound (at least one)	yes	214[a]	48%
	no	231	52%
Urine test (at least one)	yes	280[a]	62.90%
	no	165	37.10%
Hemoglobin test (at least one)	yes	294[a]	66%
	no	151	34%

[a] Adequate ANC utilization was identified in 213 (47.9%) pregnant women defined for those who had **all** the following criteria: ANC 4 or more contacts (+) first booking during the first trimester (+) at least one ultrasound (+) at least one urine test (+) and no less than one hemoglobin test

Of note, from the adequate ANC utilization group, a "complete" ANC utilization was found in 22 pregnant women who had all the following: attended ANC clinic eight or more times, first booking in the first trimester, had at least one ultrasound, had at least two urine tests, and performed no less than two hemoglobin tests.

Antenatal care utilization – Univariable analysis

The results of the univariable analysis (Table 3) showed a statistically significant association between adequate ANC service utilization and the age of the mother, residence, household sanitation and pregnancy planning.

The results indicate that in the unadjusted analysis the crude odds (COR) of adequate ANC utilization increased approximately twice for women who were within the age group of 20–34 years (COR 2.25; 95% CI: 1.37- 3.70) and 35 years and above (COR 2.12; 95% CI: 1.13–3.98) compared to women in the 14–19 age group. The odds of having adequate ANC service utilization increased approximately twice for women from households with sanitation (COR 2.19; 95% CI: 1.49–3.21) and living in urban areas (COR 1.98; 95% CI: 1.36–2.91) and increased 2.68 times for women who planned the pregnancy (COR 2.68; 95% CI: 1.69 to 4.24).

Antenatal care utilization – Multivariable analysis

In Table 4, the results obtained from the multivariable logistic regression model are depicted, show the adjusted associations strength between the factors that remained in the final model and ANC utilization. The results obtained from the multivariable logistic regression

Table 3 Determinants associated with ANC utilization in univariable logistic regression analyses among pregnant women admitted at Hospital Dr Ayres de Menezes, Sao Tome & Principe

	ANC service utilization			
	Adequate	**Partial**	**COR [95% CI]**	***p* value**
	***n* = 213 (47.9%)**	***n* = 232 (47.9%)**		
Age				
14–19	30 (32.6%)	62 (67.4%)	1.00	
20-34	145 (52.2%)	133 (47.8%)	2.25 [1.37 to 3.70]	**0.001**
35+	33 (50.7%)	37 (49.3%)	2.12 [1.13 to 3.98]	**0.019**
Education				
none	7 (50%)	7 (50%)	1.00	
Primary	104 (41.6%)	146 (58.4%)	0.71 [0.243 to 2.09]	0.537
Secondary	78 (52.7%)	70 (47.3%)	1.11 [0.372 to 3.34]	0.847
higher	24 (72.7%)	9 (27.3%)	2.67 [0.728 to 9.76]	0.139
Employment				
not working	139 (45.3%)	168 (54.7%)	1.00	
working	74 (54.8%)	61 (45.2%)	1.46 [0.99 to 2.20]	0.065
Marital status				
union/married	181 (48.9%)	189 (51.1%)	1.22 [0.72 to 2.07]	0.456
Single	29 (43.9%)	37 (56.1%)	1.00	
Father education				
none	4 (40%)	6 (60%)	1.00	
primary	65 (44.5%)	81 (55.5%)	1.2 [0.33 to 4.45]	0.781
Secondary	61 (53.5%)	53 (46.5%)	1.73 [0.46 to 6.45]	0.417
higher	24 (68.6%)	11 (31.4%)	3.27 [0.77 to 13.99]	0.110
Residence				
Urban	116 (57.4%)	86 (42.6%)	1.98 [1.36 to 2.91]	**< 0.001**
Rural	95 (40.4%)	140 (59.6%)	1.00	
Household sanitation				
open defecation	76 (37.6%)	126 (62.4%)	1.00	
Sanitation	136 (56.9%)	103 (43.1%)	2.19 [1.49 to 3.21]	**< 0.001**
Parity				
0	64 (47.1%)	72 (52.9%)	1.71 [0.80 to 3.62]	0.161
1–4	136 (50.2%)	135 (49.8%)	1.94 [0.95 to 3.94]	0.068
5 +	13 (34.2%)	25 (65.8%)	1.00	
Pregnancy				
Unplanned	103 (40.9%)	149 (59.1%)	1.00	
Planned	74 (64.9%)	40 (35.1%)	2.68 [1.69 to 4.24]	**< 0.001**
Previous contraceptive use				
Yes	46 (51.1%)	44 (48.9%)	1.16 [0.72 to 1.86]	0.549
No	132 (47.5%)	146 (52.5%)	1.00	

Abbreviations: *COR* Crude odds ratio, *CI* Confidence interval

1.00 Reference categories

model, showed the adjusted (AOR) association strength between the factors that remained in the final model and adequate ANC service utilization.

In the multivariable logistic regression, mothers' age, residence, and pregnancy type of planning continued to have an association with adequate ANC service utilization. The results indicate that women in the 20–34-year age group (AOR 2.28; 95% CI: 1.28–4.04; $p = 0.005$) and those 35 years old or above (AOR 2.51; 95% CI: 1.21–5.20; $p = 0.013$), living in urban areas (AOR 1.98; 95% CI: 1.28–3.06; $p = 0.002$) and with a planned pregnancy (AOR 2.59; 95% CI: 1.60–4.18; $p < 0.001$) are more likely to have

Table 4 Multivariable logistic regression analyses of the determinants associated with adequate ANC utilization among pregnant women admitted at Hospital Dr Ayres de Menezes, Sao Tome & Principe

Variable		AOR	95% CI	*p*-value
Age	20–34	2.28	1.28 to 4.04	0.005
	35 +	2.51	1.21 to 5.20	0.013
	14-19[a]			
Residence	Urban	1.98	1.28 to 3.06	0.002
	Rural[a]			
Pregnancy	Planned	2.59	1.60 to 4.18	<0.001
	Unplanned[a]			

Abbreviations: *AOR*, adjusted odds ratio; *CI* confidence interval

[a] Reference categories

adequate ANC service utilization. A p value = 0.810 was obtained by the Hosmer–Lemeshow test indicating that the model was well calibrated.

Discussion

ANC coverage in STP is a success compared to other SSA countries [10, 16, 19–21]. Attendances are extremely high for a low-resource country, as we found that 85.1% of the participants had four or more visits when rates reported in SSA are approximately 62% [17]. However, this high number of contacts are not equivalent to provision of good practice interventions as this study highlights that more than half of the pregnant women enrolled doesn´t have at least one evidence-based screening test, such as hemoglobin, urine, and obstetric ultrasound. Adequate utilization, meaning that a pregnant woman had four or more ANC contacts, an early booking, had one obstetric ultrasound, and tested for hemoglobin and urine at least once, was only meet by 47.9%.

Our univariable analysis revealed some associations with the factors known to influence ANC utilization with a significant association between women's age and adequate ANC utilization, as shown in other studies [1, 8, 13]. For example, the higher the age of the expectant mother, the more she would adequately utilize ANC [1, 13]. The same is true for adolescent girls (14–19 years) who are more likely to have partial ANC utilization, probably due to lack of adequate knowledge of essential aspects of ANC service and misconceptions compared to older women [18, 19]. Other reasons for this behavior may be delay in recognizing of the pregnancy status, shame, or negative feelings towards an unwanted pregnancy [12, 18–20]. These findings are similar to those published for other countries in SSA, as it is known that a significant number of pregnant adolescents do not access or do not adequately use ANC services [18] Addressing adolescents´ special pregnancy needs is essential to improve maternal and newborn health in the country [12, 18, 19].

Participants' educational level was also found to be a strong predictor of adequate ANC utilization. Mothers-to-be who had higher education were more likely to have adequate ANC utilization than their lower educated counterparts. This is not counter-intuitive because previous studies in low-resource countries have reported that the educational level of women increases the odds of having four or more ANC contacts [17, 20–23]. Nonetheless, it should be said that 5.4% of this study´s expectant mothers had less than 16 years old and 14.7% between 17 and 19, meaning that almost 20% of the participants were not old enough to reach a higher education opportunity. The major cause of health inequality in ANC coverage has been strongly associated with a lack of knowledge together with cultural, social, and religious factors [22]. Therefore, reinforcement of women´s education is crucial, as it promotes a better knowledge of maternal and newborn health-related issues [13, 24].

Residence area is another factor with influence [13, 23, 25, 26]. The odds of an adequate ANC utilization increase among urban women, as found in similar studies in low-resource countries [1, 14, 22, 25–27]. In Sao Tome and Príncipe all rural areas have one district maternity available with basic obstetric care and pregnancy follow-up. Thus, different from other studies, this cannot be explained by the lack of these infrastructural facilities or in terms of a far distance. According to published data, in STP, 74% of households have access to health services within 30 min or less, although there are discrepancies between urban areas (87%) and rural areas (59%) [9]. These disparities could be associated with less access to information on pregnancy-related issues compared to their urban counterparts. Household with sanitation showed a significant relationship with ANC utilization, as women from these households have higher odds of utilizing ANC adequately than those practicing open defecation [13]. This finding is probably linked to mother´s wealth and indirect financial autonomy for paying pregnancy exams [28–30].

The results further show that the odds of ANC utilization are higher among working women than non-working women, although without statistical significance [13, 31, 32]. This may be also linked to the ability to pay ANC since working women have their own financial autonomy and are not dependable on their husband/partner or family [29].

Moreover, the rate of adequate utilization of ANC is higher among women with a planned pregnancy. The possible reason might be that pregnant women with a

planned pregnancy are much more cautious and eager to know their pregnancy progress than those who had unplanned or unintended pregnancy [21, 29]. Usually, planned pregnancies are safer for the mother and deliver healthier babies, hence, the awareness and the capacity to choose to become pregnant must be a reality to be reinforced [22, 29, 33, 34].

A previous use of contraceptives was found to be associated with adequate ANC utilization, although no statistical significance was established. In STP, most women use traditional (natural) family planning methods as part of a system of traditions that is passed down from generation to generation through the teaching of certain beliefs [9, 10]. We found that only twenty percent of mothers-to-be had a previous contraceptive use, highlighting the need to reinforce the importance of family planning in the country. Incentives should also be made for spacing children as this can reduce mortality among under-fives by 10% and among pregnant mothers by 32% [22]. Thus, family planning services should be enhanced as it promotes small family size, improves child survival, and reduces sibling competition for scarce family and maternal resources [22, 24, 35–37].

These risk factors were also analyzed in other studies conducted by the authors within the context of a broader research on the causes and risk factors contributing to neonatal mortality and adverse birth outcomes in Sao Tome & Principe [38–42].

All the previous findings were obtained in the univariable study. However, in the multivariable analysis only some of the factors remained in the final model. Accordingly, determinants of an adequate ANC utilization in this study were maternal age greater than twenty years (sociodemographic characteristic), urban residence (community level characteristics), and a planned pregnancy (pregnancy related characteristic).

Strengths and limitations of the study

This study included data with a total number of pregnant women similar to the one recently published for the country in 2019 Multiple Indicator Cluster Survey (MICS) from UNICEF [10]. In contrast to MICS, our study is not the object of recall bias because the data were gathered during the current pregnancy through interviews and data abstraction from ANC pregnancy cards.

Another main strength is that this study included essential routine screenings (obstetric ultrasound, hemoglobin, and urine tests) in addition to the number of contacts per pregnant woman and an early booking during the first trimester. In contrast to most studies in SSA countries that only analyze ANC utilization in terms of the ANC number of contacts and/or timing [12, 13].

This study was conducted in the capital city and may overestimate actual ANC visits as attitudes and practices may differ from rural areas in terms of access to health care, health worker motivation and training, and availability of health services. Factors such as women´s autonomy and the impact of media exposure were not assessed in this study, missing out some determinants associated to ANC utilization, such as sociocultural beliefs and convictions that sometimes dissuade women from accessing the antenatal care services [14].

Future studies

Further research is needed to determine the effects of traditional, sociocultural, religious, and other related practices at the community-level on the utilization of ANC services. Another important subject would be to determine the extent to which real family planning counseling takes place during ANC visits.

Conclusion

Less than half of the pregnant women reached adequate ANC utilization, highlighting the challenge still ahead for ANC optimization in Sao Tome & Principe. The present study showed that the determinants of an adequate ANC utilization were maternal age greater than twenty years, urban residence, and a planned pregnancy. Understanding pregnant women´s determinants of ANC utilization in view of improving it is an excellent bridge to achieve its optimization. Measures such as raising awareness of the importance of ANC screenings completion, engaging the more vulnerable women in earlier utilization of family planning services, and promoting each women empowerment for a pregnancy plan are key strategies to improve neonatal health outcomes in the country.

Abbreviations

STP	Sao Tome & Principe
HAM	Hospital Dr. Ayres de Menezes
OR	Odds Ratio
CI	Confidence Interval
SDG	Sustainable Development Goal
ANC	Antenatal care
MICS	Multiple Indicator Cluster Survey
WHO	World Health Organization
FANC	Focused Antenatal Care

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Authors' contributions

AV carried out the conception and design of the study, data collection and wrote the manuscript. MCM and FP critically evaluated and made progressive suggestions throughout the study and revised the manuscript. MA and ALP performed

the statistical analysis. NB and SS were involved in the study design at the country level. All the authors read and approved the final draft of the manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are all available within the manuscript itself.

Declarations

Ethics approval and consent to participate
The study was approved and consented to by the Ministry of Health of Sao Tome & Principe and by the main board of Hospital Dr. Ayres de Menezes, since at the time the study protocol was submitted there were no ethics committees in Sao Tome & Principe. Only recently has the country National Ethics Committee been appointed. Previously, study analysis and approval were done by the Ministry of Health and the institution where the study was to be performed, which is what we have done. All methods were performed in accordance with the relevant guidelines and regulations in practice. Written informed consent was obtained from all participants (or their parent or legal guardian in the case of adolescents under 16) after the purpose of the research was explained orally by the main investigator. Additionally, if the mother was illiterate and unable to write, oral consent was given in the presence of at least one witness, usually the ward nurse´s complementarity to the mother´s fingerprint mark in the consent form. Participation in the survey was voluntary, as participants could decline to participate at any time during the study. The anonymity and safety of participants were ensured.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Research Article

Intestinal Parasitic Infections, Treatment and Associated Factors among Pregnant Women in Sao Tome and Principe: A Cross-Sectional Study

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Background. Intestinal parasitic infections (IPIs) are a public health problem in developing countries such as Sao Tome and Principe (STP) although the pregnancy burden of IPIs is unknown in this endemic country. Thus, the aim of this study was to determine the prevalence of IPIs, prescribed anthelmintics, and associated factors among pregnant women admitted to Hospital Dr. Ayres de Menezes (HAM). *Methods*. A hospital-based cross-sectional study was conducted among pregnant women admitted to the HAM who had undergone antenatal copro-parasitological screening. Data were abstracted from antenatal care (ANC) cards regarding parasitological results and anthelmintic prescriptions. A structured questionnaire face-to-face interview was also applied. Pregnant women with an IPI (210) were compared to noninfected women (151). Data analysis was performed using SPSS version 25.0. Odds ratios (ORs) with 95% confidence intervals (CIs) for factors associated with IPIs were estimated using multiple logistic regression models. A p value <0.05 was considered statistically significant. *Results*. A total of 361 participants (210 IPI and 151 no-IPI) with a mean age of 26.96 (SD: 7.00) were included. The overall prevalence of IPI was 58.2% (95% CI 52.9 to 63.3), mainly due to helminthiasis, with a 55.9% (95% CI 50.7–61.2%) rate. *Ascaris lumbricoides* (90.9%) was the most predominant parasite species identified followed by *Trichuris trichiura* (13.8%). Polyparasitism was observed in 25 cases (11.9%). Anthelmintics were prescribed to 23% of pregnant women. *S intercalatum* (11) and *E histolytica* (7) infections were not adequately treated. IPI was significantly associated with primary education (AOR 1.73 (95% CI: 1.10–2.71)), unemployment (AOR 1.94 (95% CI: 1.20–3.13)), and parity of five or above (AOR 3.82 (95% CI: 1.32–11.08)). *Conclusion*. This study highlights the IPI burden, associated factors, and missing treatment opportunities among pregnant women with STP. This study is a useful tool for policymakers in STP to enhance the health of women and their unborn babies.

1. Introduction

Intestinal parasitic infections (IPIs) are neglected tropical diseases (NTDs) and a burden to pregnant women, with a prevalence that ranges from 24 to 70% in low- and medium-income countries (LMICs), with rates of coinfection with different parasites (polyparasitism) of approximately 10% [1]. Globally, among pregnant women, the most common infestation is hookworm and whipworm (*Trichuris trichiura*), followed by *Ascaris lumbricoides* [1–4].

Less frequent but also prone to cause adverse birth outcomes and complications during pregnancy are invasive enteric parasites such as Schistosoma *spp*. and the protozoan *Entamoeba histolytica* [1]. Schistosomiasis affects

approximately 200 million people and is "second only to malaria in public health importance," with pregnant women being one of the important at-risk groups [5, 6]. *Entamoeba histolytica*, responsible for amebiasis, remains one of the top three parasitic causes of mortality, with an estimated 50 million people affected worldwide [7, 8].

The major concerns regarding IPI in pregnant women are the associated higher risks for adverse maternal outcomes, such as anemia as well as poor pregnancy weight gain [9–11]. Additionally, IPI implications in newborn health are the risk of low birth weight (LBW), intrauterine growth retardation, prematurity, stillbirths, and neonatal mortality, a considerable burden in countries that already have a high rate of neonatal mortality and morbidity [12–14].

Regarding the anthelmintic treatment of IPI during pregnancy, there is still some controversy [15, 16], although it is endorsed by the World Health Organization (WHO) [17–19]. The most recommended drugs for treating IPI in pregnancy are albendazole for helminths, praziquantel for Schistosoma, and metronidazole for protozoan parasites [20, 21]. Nonetheless, available evidence shows that most pregnant women in IPI-endemic settings do not receive any deworming medication, with the WHO setting a target of reaching a 75% rate of deworming pregnant women by 2030 [3, 22].

Knowing each country's reality and specific associated factors promoting IPI among pregnant women will allow us to tackle it more accurately. In general, factors associated with IPIs are intimately connected with poverty and are the same for both the general population and pregnant women [23]. For instance, a well-known independent risk factor is WASH, an acronym for inadequate water supply, sanitation, and hygiene, which is also the major factor responsible for mortality and burden of disease due to diarrhea-causing infections in LMICs [24, 25].

Sao Tome and Principe (STP) is the second smallest African country, a low-income setting, endemic for helminthiasis and schistosomiasis (*S intercalatum*) [26, 27]. The current country strategy is preventive IPI chemotherapy to be given only to preschool and school-aged children [28]. Infected pregnant women receive anthelmintic treatment in the second or third trimester on a case-by-case basis although the country's prevalence of anemia among pregnant women is around 61% [29].

To our knowledge, intestinal parasitic infections among pregnant women in Sao Tome and Principe have never been studied. This study was undertaken within the context of a broader project on the causes and risk factors contributing to neonatal mortality and adverse birth outcomes in STP [30, 31].

We sought to determine the prevalence of IPIs, prescribed anthelmintics, and associated factors among pregnant women admitted to Hospital Dr. Ayres de Menezes.

Thus, these research findings will help to design targeted interventions for these NTDs among pregnant women in STP and better allocate resources to where they are needed.

2. Materials and Methods

2.1. Study Design. A hospital-based cross-sectional study was carried out on pregnant women admitted to the HAM maternity unit for delivery.

2.2. Setting. The archipelago of Sao Tome and Principe is an African island nation, with 219,161 inhabitants [29]. The level of poverty is high, with 47% of the population practicing open defecation and only 69.8% having access to clean and safe drinking water [29].

This study was conducted at the HAM maternity unit, which has an annual average delivery rate of 4500 births, approximately 82.4% of all deliveries in the country, as it is the only hospital in the country. Antenatal care (ANC) coverage in STP is high, and women are asked to perform a routine copro-parasitological exam during the pregnancy period. The exam consists of stool sampling using the direct wet mount method and formol-ether concentration method and then observation by trained parasitologists who declare it positive when various stages of the parasites, such as trophozoites, cysts, ova, and larvae, are identified. The results from copro-parasitological exams, as well as prescribed anthelminthics, are registered by the nurses in the ANC pregnancy card that pregnant women carry along all ANC visits and bring to the HAM at the time of labor.

2.3. Participants. All pregnant women admitted to the HAM maternity unit for delivery constituted the source population, whereas the study populations were selected pregnant women admitted to the HAM maternity unit during the study period. The recruitment occurred from July 2016 to November 2018.

2.4. Eligibility Criteria. All women admitted to the HAM maternity unit for delivery with a gestational age of 28 weeks or more were eligible to be enrolled in the study. Those who gave birth in the rural basic maternity units but were immediately transferred to HAM for postpartum medical evaluation or newborn follow-up were also eligible to be included in the study.

The exclusion criteria included the following: (1) pregnant women with gestational age less than 28 weeks, (2) women who had no ANC pregnancy card, (3) women with cognitive impairment, (4) women who were unstable due to postpartum complications, and (5) adolescent or illiterate mothers who had not obtained permission from their parents or legal guardians to participate in the study. Pregnant women without ANC copro-parasitological screening (147) and pregnant women with HIV, sickle cell disorder, and malaria (10) were also excluded from this study.

A total of 361 pregnant women with a copro-parasitological exam performed during the ANC period and with the result registered in the pregnant ANC card were included. Pregnant women were divided into two groups, pregnant women with intestinal parasite infection (at least one) versus those without any IPI for associated factor assessment. A flowchart of participation in the study is shown in Figure 1.

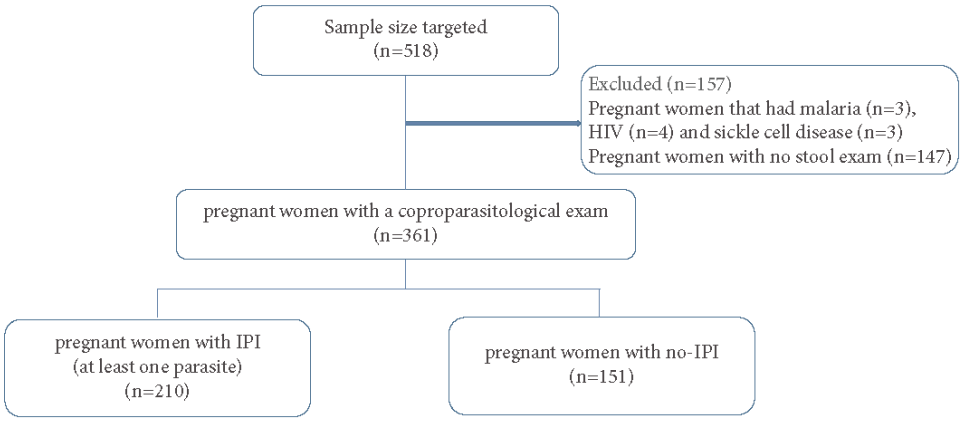


Figure 1: Flowchart of participation in the study.

2.5. Sampling Method. The software used for sample calculation was Raosoft (http://www.raosoft.com/samplesize.html), and a minimum sample size of $S = 355$ was recommended. For the original study, participants were enrolled based on the following assumptions: a two-sided 95% confidence level and a power of 80% to detect an odds ratio of at least two for neonatal adverse birth outcomes. Since the sample size was not calculated for the present outcomes, a power analysis was performed, varying from 79% to 89% for this study.

Pregnant women were selected randomly until the required sample size was achieved. Participants were invited to participate in the study after admission to the maternity unit of HAM. Each day, from the pile of admission folders, every second interval folder was selected and then carried on asking for consent for enrollment. Women's consent to participate in the study was obtained at the time of admission at HAM, but the interview was held after a woman was stabilized and ready to be discharged.

2.6. Data Source. The data source for this study consisted of data abstracted from the ANC pregnancy card plus a face-to-face interview. The ANC pregnancy card of each study participant was used to collect information such as the copro-parasitological result and anthelmintic prescription. Data on the sociodemographic characteristics of the participants were gathered using a structured questionnaire through a face-to-face interview with the main investigator before the women were discharged. Issues covered included the mother's and father's socioeconomic characteristics and reproductive history. All data were recorded in the app survey tool.

2.7. Study Variables. The exposure variables in this study include major parasitic infections as recorded in the ANC pregnancy card, such as helminthiasis (*Ascaris lumbricoides*, *Trichuris trichiura*, *Ancylostoma duodenale*, and *Strongyloides stercoralis*), schistosomiasis (*Schistosoma intercalatum*), and protozoans as amebiasis (*Entamoeba histolytica*).

Polyparasitism was defined as the presence of two or more parasite species in the same host.

The sociodemographic variables studied were as follows: (i) maternal age, (ii) maternal education, (iii) maternal occupation, (iv) marital status, (v) number of antenatal care visits, and (vi) area of residence. Mother occupation variable was categorized into two groups: employed (professional and service) and unemployed (housewife, farmer, business, and student). Education was included as a categorical variable: no education, primary education, secondary education, and higher education. The residence was defined as urban or rural, the first when women were living in the capital city (Água Grande) and rural in all other districts. We also analyzed hygiene and sanitation variables such as having access to improved water and type of toilet (toilets with flush and pit latrines) or open defecation. Parity was categorized as nullipara (0), multipara (1–4), and grand multipara (5 or above).

2.8. Data Quality Control. The questionnaires were administered in Portuguese, the national language. Continuous follow-up and supervision of data collection were made by the supervisors. The collected data were checked daily for completeness. The field investigator (a pediatrician) executed and was responsible for the main activities as follows: (1) obtaining consent and enrollment of the mothers, (2) face-to-face interviews, (3) abstraction of data from antenatal pregnancy cards, and (4) data entry into the app survey tool.

2.9. Statistical Analyses. Data analysis was carried out in three stages. The first stage involved pooling data for descriptive statistics with categorical variables being presented as frequencies and percentages and quantitative variables as the mean and standard deviation. In the second stage, the chi-square test and Fisher's exact test were used to describe the relationship between pregnant women with IPI and the categorical explanatory variables. The third stage involved a univariable analysis to identify the candidate variables for the multivariable analysis (with a p value <0.25). In all these

analyses, logistic regression models were applied. Linearity in the logit assumption of age was verified with generalized additive regression models. Crude odds ratios (CORs) and adjusted odds ratios (AORs) with corresponding 95% confidence intervals (95% CI) were estimated. The level of significance $\alpha = 0.05$ was considered. All data were entered into QuickTapSurvey (2010–2021 Formstack) and further analyzed using the Statistical Package for the Social Sciences for Windows, version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

2.10. Ethics Approval and Consent to Participate. The study complies with the Declaration of Helsinki and was approved and consented to by the Ministry of Health of Sao Tome and Principe and by the main board of Hospital Dr. Ayres de Menezes since at the time the study protocol was submitted that there was no ethics committee in STP. Only recently has the country's National Ethics Committee been appointed. Previously, study analysis and approval were performed by dedicated ethics oversight bodies, such as the Ministry of Health of Sao Tome and Principe and the main board of the Hospital Dr. Ayres de Menezes, and both approved this study.

Moreover, all methods in our study were performed in accordance with the relevant guidelines and regulations in practice.

Written informed consent was obtained from all participants after the purpose of the research was explained orally by the researcher. Approval by the participants' parents or legal guardians was asked in the case of adolescents under 16 years of age or illiterate women.

The participants or their legal representatives also consented to have the results of this research work to be published. Participation in the survey was voluntary, as participants could decline to participate at any time during the study.

3. Results

3.1. Characteristics of the Population. A total of 361 pregnant women with a mean age of 26.96 (SD: 7.00) years old were included in this study.

Most of the participants had primary education, lived in rural areas, and were unemployed as described in Table 1. More than three-quarters of the participants were multiparous, and half had complete ANC attendance. A high proportion had access to improved water sources, and half of the pregnant women had sanitation.

3.2. Prevalence of Parasitic Infections. Of the total number of pregnant women, 210 (58.2%, 95% CI 52.9 to 63.3) were infected with at least one pathogenic parasite. The types of parasites identified in the 210 copro-parasitological specimens are presented in Table 2.

Coinfection with different parasites (polyparasitism) in the same host was observed in 25 pregnant women (11.9%), as described in Table 3.

Helminthiasis in monoparasitic infections (with *Ascaris lumbricoides*, *Trichuris trichiura*, *Ancylostoma duodenale*, or *Strongyloides stercoralis*) was found in 202 pregnant women, with a prevalence of 55.9% (95% CI: 50.7 to 61.2).

Schistosomiasis (*S intercalatum*) was found in 3.0% (11/361) (95% CI: 1.5 to 5.4), and amebiasis with the protozoan *E histolytica* was found in 1.9% (7/361) (95% CI: 0.8 to 3.9), including polyparasitic infections.

Regarding *S intercalatum* infection ($n = 11$), 72.7% (8) were aged 20–34 years old, 72.7% (8) had primary education, 100% (11) were married/union, 90.9% (10) had access to improved water, 63.6% (7) were living in an urban area, 54.5% (6) had sanitation, 54.5% (6) were multiparous, and 72.7% (8) had a completed ANC (8 or above visits).

3.3. IPI Pregnant Women Treatment. The anthelminthic prescriptions registered in the ANC pregnancy cards were albendazole, mebendazole, metronidazole, and piperazine. Table 4 further describes the prescription according to the type of parasite. Regarding the helminthiasis group, a total of 23.8% (46) received anthelminthic treatment. Adequate treatment prescription (albendazole, mebendazole, or piperazine) was identified in 40 pregnant women with helminthic-IPI. Five received metronidazole inadequately.

Anthelminthic prescriptions for women infected with *S intercalatum* and *E histolytica* were all identified as inadequate (Table 4).

3.4. Pregnant Women with IPI versus Pregnant Women with No-IPI. The comparison of sociodemographic characteristics between pregnant women with IPIs and those without IPIs is shown in Table 1.

3.5. Factors Associated with IPIs in Pregnant Women: Univariable Analysis. Table 5 concerns the univariable regression analysis to identify candidates for the multivariable analysis among factors for IPI during pregnancy. The results indicate that the odds of having an IPI during pregnancy increased twice for pregnant women with primary education (cOR 2.58; 95% CI 1.14–5.83; $p = 0.023$). The odds of having an IPI increased twice for unemployed women (cOR 2.03; 95% CI 1.28–3.19; $p = 0.002$). Women with a parity of 5 or above had 4.19 times higher odds of having an IPI during pregnancy (95% CI 1.49–11.79; $p = 0.006$) than nulliparous women. Women with 4 to 7 visits and those with 8 or more ANC visits were 68% (cOR 0.32; 95% CI 0.11–0.89) and 63% (cOR 0.37; 95% CI 1.13–1.04) less likely to have an IPI when compared to those with 1 to 3 ANC visits, with a statistical significance of $p = 0.030$ and $p = 0.060$, respectively.

3.6. Factors Associated with IPIs in Pregnant Women: Multivariable Analysis. The results obtained from the multivariable logistic regression model are also depicted in Table 5, showing the adjusted association strength between the factors that remained in the final model and intestinal parasite infections in pregnant women. Results indicate that

Table 1: Baseline characteristics of the study sample (361), pregnant women with IPI (210), no-IPI (151), and associations with maternal characteristics.

	Total pregnant women ($n = 361$)	IPI ($n = 210$)	no-IPI ($n = 151$)	p value*
Age				
14–19	65 (18)	39 (18.6)	26 (17.2)	0.552
20–34	233 (64.5)	131 (62.4)	102 (67.5)	
≥35	63 (17.5)	40 (19)	23 (15.2)	
Education				
None	12 (3.3)	5 (2.4)	7 (4.6)	
Primary	196 (54.3)	132 (62.9)	64 (42.4)	**0.002**
Secondary	126 (34.9)	61 (29)	65 (43)	
Higher	27 (7.5)	12 (5.7)	15 (9.9)	
Employment				
Not working	250 (69.6)	158 (76)	92 (60.9)	**0.002**
Working	109 (30.4)	50 (24)	59 (39.1)	
Marital status				0.721
Union/married	303 (85.4)	177 (85.9)	126 (84.6)	
Single	52 (14.6)	29 (14.1)	23 (15.4)	
Baby's father education				
None	8 (3.3)	3 (2.1)	5 (5)	
Primary	116 (47.3)	71 (49)	45 (45)	0.485#
Secondary	94 (38.4)	57 (39.3)	37 (37)	
Higher	27 (11)	14 (9.7)	13 (13)	
Residence				
Urban	166 (46.4)	120 (57.4)	72 (48.3)	0.089
Rural	192 (53.6)	89 (42.6)	77 (51.7)	
Water source				
Improved water	304 (84.2)	173 (82.4)	131 (86.8)	0.261
No	57 (15.8)	37 (17.6)	20 (13.2)	
Household sanitation				
With sanitation	202 (56.4)	112 (53.8)	60 (90)	0.247
Open defecation	156 (43.6)	96 (46.2)	40 (60)	
Parity				
0	103 (28.5)	57 (27.1)	46 (30.5)	**0.010**
1–4	227 (62.9)	127 (60.5)	100 (66.2)	
5+	31 (8.6)	26 (12.4)	5 (3.3)	
ANC visits				
<4	24 (6.6)	19 (9)	5 (3.3)	0.075
4–7	168 (46.5)	92 (43.8)	76 (50.3)	
≥8	169 (46.8)	99 (47.1)	70 (46.4)	

ANC: antenatal care and IPI: intestinal parasitic infection. p value <0.05 marked as bold text. * p value calculated from chi-square test.# p value calculated from Fisher's exact test.

Table 2: Parasites identified in the 210 positive copro-parasitological exams.

	Stool specimens	Frequency (n=)	Percentage* (%)
Helminths	*Ascaris lumbricoides*	191	90.9
	Trichuris trichiura	29	13.8
	Ancylostoma duodenale	3	1.4
	Strongyloides stercoralis	1	0.5
Schistosoma	*Schistosoma intercalatum*	11	5.2
Intestinal protozoans		Pathogenic	
	Entamoeba histolytica	7	3.3
	Giardia duodenalis	2	0.9
		Nonpathogenic	
	Endolimax nana	1	0.5

*parasite individual percentages add more than 100% due to copro-parasitological exams with more than one parasite per sample. Out of the 210 exams analyzed, a total of 245 different parasite specimens were identified.

Table 3: Polyparasitic infections (coinfection of two or more parasite species in the same pregnant women).

Polyparasitism	Frequency (n=)	Percentage* (%)
Ascaris lumbricoides + *Trichuris trichiura*	18	
Schistosoma intercalatum + *Entamoeba histolytica*	3	
Ascaris lumbricoides + *Ancylostoma duodenale*	2	
Ascaris lumbricoides + *Schistosoma intercalatum*	2	
TOTAL	25	11.9

*From the 210 pregnant women with an IPI, a total of 25 (11.9%) had two different parasites identified in their copro-parasitologial exam. The helminths group total 224 including polyparasitic infections (Table 2), but only 202 pregnant women had helminthic monoparasitic infection.

Table 4: ANC anthelminthics prescription registered in the ANC pregnancy cards.

IPIs treatment	Helminths (n = 202)*	*S intercalatum* (n = 11)*	*E histolytica* (n = 7)*
No	147 (72.7)	8 (72.8)	4 (57.1)
Missing	9 (4.5)	1 (9.0)	0
Yes	46 (22.8)	2 (18.2)	3 (42.9)
Anthelminthic drug			
Albendazole	20 (43.5)	0	1 (33.3)
Mebendazole	17 (37)	0	2 (66.7)
Metronidazole	6 (13)	0	0
Piperazine	3 (6.5)	2 (100)	0
Adequate prescription	40 (87)	0	0
Inadequate prescription	6 (13)	2 (100)	3 (100)

IPI: intestinal parasitic infection. *For the anthelmintic prescription analysis, three different groups were considered since the recommended drugs are different for helminthiasis (albendazole, mebendazole, or piperazine), schistosomiasis (praziquantel) [20, 32], and amebiasis (paromomycin, nitroimidazoles as metronidazole or tinidazole) [7, 8]. The sum refers to 220 infections: 202 monoparasitic helminthiasis plus 11 schistosomiasis (*S intercalatum*), and 7 amebiasis (*E histolytica*). Schistosomiasis and amebiasis coinfection cases were included. Giardiasis cases (2) were not described due to missing information on anthelmintic prescription.

women with primary education, not working and with a parity of 5 or above, are more likely to have an IPI during pregnancy.

4. Discussion

Women living in LMICs are known to have a higher risk of acquiring an IPI during their pregnancy and consequently suffering complications from these NTDs [1]. This study aimed to identify the prevalence, treatments, and associated factors among pregnant women with an intestinal parasitic infection. This study confirms a high prevalence of intestinal parasitic infection among pregnant women in Sao Tome and Principe, as the overall prevalence was 58.2% (95% CI 52.9 to 63.3). Our prevalence is higher than that in nearby countries, namely, Ghana with 23.0% [33, 34] and Nigeria with 20.8% [35], but lower than that in other countries, such as Ethiopia, where it reaches 70.6% [36–38].

Soil-transmitted helminths (STHs) or geohelminths were the main IPI group among pregnant women enrolled in our study, in contrast to Ghana, which reports higher rates of intestinal protozoans [34].

Although higher in our study (90.9%), other studies from endemic countries also found a preponderance of *Ascaris lumbricoides* among pregnant women, such as Venezuela with 57% [13], Ethiopia with 32.7% [36], and Kenya with 6.5% [39]. In STP, previous data concerning IPI among children reported up to an 86.7% rate of infection, mainly with *Ascaris lumbricoides* (56.3%) and *Trichuris trichiura* (52.5%), reinforcing a previously existing high burden of helminthiasis in the country [38]. Therefore, these high rates of ascariasis and trichuriasis in STP illustrate that transmission occurs due to soil and domestic water supply with fecal pollution around homes with poor sanitation and improper sewage disposal [39].

In contrast, a very low rate of hookworm (1.4%) and strongyloidiasis (0.5%) in comparison to other studies [37, 38] was found, probably due to infrequently walking barefoot among the adult population in the country preventing larvae penetration in the feet skin [1, 37].

Regarding schistosomiasis, we found a 3% prevalence of *S intercalatum*. Overall estimates report that 10 million women in Africa per year have schistosomiasis during pregnancy although we could not find any study regarding *S intercalatum* infection in pregnant women in literature [40, 41]. This paucity of data can be related to the fact that *S intercalatum* is restricted to a few central African countries, is transmitted by *Bulinus forskalii*, and has a mild pathogenicity linked to rectal schistosomiasis and minor liver pathology [32, 42]. We observed that most pregnant women from our study with an *S intercalatum* infection had an urban residence. This "urbanization" of *S intercalatum* was previously reported in another study from central Africa [43]. This "urban" transmission of schistosoma occurs while walking through flooded streets (temporary snail breeding sites) instead of the traditional transmission in rural areas when people become infected through contact with parasite-harboring snails in natural water sources during activities such as fishing, farming, or swimming [44].

Concerning *Entamoeba histolytica*, a lower rate of 1.9% was found in this study compared to other settings, such as Venezuela, with a 12% rate [13]. Other intestinal protozoa,

Table 5: Results of univariable and multivariable logistic regression analysis regarding IPI associated factors.

	IPI ($n = 210$)	no-IPI ($n = 151$)	cOR (95% CI)	p value	AOR (95% CI)
Age					
14–19	39 (18.6)	17.2 (26)	1		
20–34	131 (62.4)	67.5 (102)	0.86 (0.48–1.49)	0.587	
≥35	40 (19)	15.2 (23)	1.16 (0.57–2.37)	0.685	
Education					
None	5 (2.4)	4.6 (7)	0.89 (0.23–3.53)	0.872	
Primary	132 (62.9)	42.4 (64)	2.58 (1.14–5.83)	**0.023**	1.73 (1.10–22.71)*
Secondary	61 (29)	43 (65)	1.17 (0.51–2.71)	0.708	
Higher	12 (5.7)	9.9 (15)	1		
Employment					
Not working	158 (76)	60.9 (92)	2.03 (1.28–3.19)	**0.002**	1.94 (1.20–3.13)**
Working	50 (24)	39.1 (59)	1		
Marital status					
Union/married	177 (85.9)	84.6 (126)	1		
Single	29 (14.1)	15.4 (23)	0.89 (0.49–1.62)	0.721	
Baby's father education					
None	3 (2.1)	5 (5)	0.56 (0.11–2.81)	0.479	
Primary	71 (49)	45 (45)	1.46 (0.63–3.40)	0.374	
Secondary	57 (39.3)	37 (37)	1.43 (0.60–3.38)	0.415	
Higher	14 (9.7)	13 (13)	1		
Residence					
Urban	120 (57.4)	72 (48.3)	1		
Rural	89 (42.6)	77 (51.7)	1.44 (0.95–2.2)	0.089	
Water source					
Improved water	173 (82.4)	131 (86.8)	1		
No	37 (17.6)	20 (13.2)	1.40 (0.77–2.53)	0.262	
Household sanitation					
Sanitation	112 (53.8)	60 (90)	1		
Open defecation	96 (46.2)	40 (60)	1.29 (0.84–1.97)	0.247	
Parity					
0	57 (27.1)	46 (30.5)	1		
1–4	127 (60.5)	100 (66.2)	1.03 (0.64–1.64)	0.918	
5+	26 (12.4)	5 (3.3)	4.19 (1.49–11.79)	**0.006**	3.82 (1.32–11.08)*
ANC visits					
<4	19 (9)	5 (3.3)	1		
4–7	92 (43.8)	76 (50.3)	0.32 (0.11–0.89)	**0.030**	
≥8	99 (47.1)	70 (46.4)	0.37 (0.13–1.04)	**0.060**	

p value <0.05 marked as bold text; *at a p value <0.02, and ** at a p value <0.001. IPI: intestinal parasitic infection.

such as *Giardia duodenalis*, were also very uncommon (0.9%) in our study, perhaps due to methodological limitations in their identification since a previous study in the country, using molecular methods (PCR), found a 7.5% prevalence of *Giardia duodenalis* among children attending HAM [45].

Looking into the associated factors of intestinal parasitic infection, we identified that education, parity, and employment were significantly associated with IPI among pregnant women in this study. Primary education increased the odds of IPI in pregnant women, in accordance with other studies from Ethiopia [37] and Kenya [10], since better education is related to enhanced health-seeking behavior. The odds of IPI were almost twofold higher in unemployed pregnant women than in those employed. This relationship between unemployment and IPIs was already reported in other studies, reinforcing that a low economic standard, typically associated with unemployment, promotes IPIs in endemic settings [46, 47].

The odds of IPI were approximately four times higher among pregnant women with a parity of five or above, consistent with other studies that reported that age and parity were possible risk factors for parasitosis [1]. For instance, ascariasis in pregnancy was found to be most common in women between 20 and 29 years of age, and the prevalence increased with parity [1], similar to our study. In contrast, other authors state that multiparous women had reduced odds of IPIs compared to nulliparous women with the rationale that they might have experienced more ANC education on how to avoid IPIs in their previous pregnancies [33]. Our findings suggest a child-driven intrafamily transmission of parasites in STP since grand multiparous women have more children, which is in accordance with previous studies that described a high burden of IPI among children in STP [48].

Open defecation and not having access to improved water were associated with an IPI higher risk although no statistically significant difference was found. While the

findings are in line with those reported from studies in Ghana [34], Colombia [49], and Mexico [50], they are contrary to those from Ethiopia [37], where the unavailability of toilet facilities was found to be significantly associated with IPI in pregnancy. Beyond this lack of association, we identified that more than 40% of all participants in this study reported having a daily practice of open defecation. Thus, Sao Tome and Principe will surely benefit if it takes the first step on the "sanitation ladder" proposed by the World Health Organization Program for Water Supply and Sanitation toward better health for all in the country [25].

Our analysis regarding anthelmintic prescription to infected pregnant women highlights that most were not treated at all, adverting to important "treatment missing opportunities." This can be due to issues related to anthelmintic safety, namely, fear of teratogenic effects by health professionals and pregnant women, a significant obstacle also reported in other endemic countries [51].

Additionally, this study also reveals the high proportion of inadequate anthelmintic prescriptions. Regarding STH infection, most pregnant women received the recommended drugs (albendazole or mebendazole) although some still received metronidazole, which is specific to protozoan infection [1]. None of the pregnant women with *S intercalatum* infection took the recommended praziquantel (40 mg/kg), and two women were even inadequately treated with piperazine [20, 32]. Similarly, pregnant women infected with *E histolytica* were not treated, even though amebiasis treatment should be warranted even in asymptomatic carriers, not only because of the potential of developing the invasive disease but also to diminish the spread of disease [7, 52, 53].

The "treatment missing opportunities" identified by this study should be urgently addressed, first by training health professionals on proper prescription, and second, in case of pregnant women refusal of treatment during the pregnancy period, they should be referred and followed up for adequate treatment in the postpartum period.

As this is the first study in Sao Tome and Principe to provide comprehensive data concerning the burden of intestinal parasites among pregnant women, recommendations from the study will assist government health officials in policy development. Public health education and awareness campaigns combined with health professionals' education programs would also enhance women's knowledge of IPI prevention and ensure adequate anthelmintic therapeutic practices by health professionals.

4.1. Limitations. Although the study was conducted at a referral center (HAM) which serves most pregnant women in Sao Tome and Principe, its findings cannot be generalizable to other areas. Rural antenatal care services in STP may have a higher prevalence of IPIs among pregnant women since they are more exposed to potential sources of infection, such as contaminated water, farm animals, and wildlife [45]. In addition, they may also have distinct behavior and poorer hygiene practices and sanitation, increasing their risk of infection in comparison with urban pregnant women [45].

5. Conclusions

Intestinal parasitic infections are a high burden for pregnant women in Sao Tome and Principe, mainly for those with primary education, unemployed, and grand multiparous. Missing opportunities for IPI treatment, mainly for *S intercalatum* and *E histolytica*, should be addressed with health professionals' training and through the follow-up of women who refuse anthelmintic drugs during pregnancy for later postpartum treatment.

Abbreviations

STP: Sao Tome and Principe
HAM: Hospital Dr. Ayres de Menezes
OR: Odds ratio
CI: Confidence interval
ANC: Antenatal care
WHO: World Health Organization
NTD: Neglected tropical diseases
LBW: Low birth weight.

Data Availability

The datasets used and/or analyzed during the current study are all included within the manuscript itself.

Ethical Approval

The study complies with the Declaration of Helsinki and was approved and consented to by the Ministry of Health of Sao Tome and Principe and by the main board of Hospital Dr. Ayres de Menezes since at the time the study protocol was submitted there was no ethics committee in STP. Only recently has the country's National Ethics Committee been appointed. Previously, study analysis and approval were carried out by the Ministry of Health and the institution where the study was to be performed, which is what the authors have carried out. All methods were performed in accordance with the relevant guidelines and regulations in practice.

Consent

Written informed consent was obtained from all participants (or their parent or legal guardian in the case of an adolescent under 16 or illiterate) after the purpose of the research was explained orally by the investigator. Participation in the survey was voluntary, as participants could decline to participate at any time during the study.

Disclosure

The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

AV, MCM, and FP carried out the conception and design of the study. AV was responsible for field activities, data collection, and wrote the manuscript. MCM and FP critically evaluated and made progressive suggestions throughout the study and revised the manuscript. MA and ALP performed the statistical analysis and reviewed the manuscript. SS and NB were involved in the study design at the country level. All the authors read and approved the final draft of the manuscript.

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Intestinal parasitic infections and adverse outcomes among pregnant women and their newborns in Sao Tome & Principe: a hospital-based cross-sectional study

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Abstract

Background

Intestinal parasitic infections (IPIs) pregnancy-related adverse birth outcomes (ABOs) remain unclear, with gaps to address. This study sought to identify the impact of IPIs among maternal-neonatal dyads in Sao Tome & Principe.

Methods

A hospital-based study was conducted among women admitted for delivery, who had a copro-parasitological screening. Confounders excluded: HIV, sickle cell, malaria and anthelminthic-treatment. Data were abstracted from antenatal cards, newborn records, and questionnaires. The infected-group (n=210) was compared to the noninfected-group (n=151). Subgroup-analyses were conducted: combined-helminths (n=202, 90.9% *Ascaris lumbricoides*), *Schistosoma intercalatum* (n=11) and *Entamoeba species* (n=7). A p-value<0.05 was considered statistically significant.

Results

A total of 361 women with a mean age of 26.96 (SD:7.00) were included; 39.6% (127) had anaemia. Among their offspring, 8.1% (26) were premature, 14.9% (48) low-birth-weight, 2.5% (8) stillbirths. No statistically significant differences (p=0.182, p=0.175, p=0.07, p=0.275) in anaemia, prematurity, low-birth-weight or stillbirths were found between the monoparasitic-subgroup and the noninfected-group. Low-birth-weight comparison between the helminths-subgroup (11.7%) and noninfected-group (19.2%) had a p-value=0.067.

Conclusion

IPI in our population was not associated with ABOs; in contrast, babies from helminthic-infected-mothers tended to have fewer low-birth-weights. In this setting, the decision to treat should be based on the impact of the IPI on the pregnant-foetus on an individual-basis.

Keywords: helminths, *Schistosoma intercalatum*, *Entamoeba species*, maternal anaemia, adverse birth outcomes, stillbirth, prematurity, low-birth-weight

Background

Intestinal parasitic infections (IPIs) are neglected tropical diseases (NTDs), with a prevalence of up to 70% among pregnant women.[1] High-burden IPIs are considered an important public health problem in endemic countries, although they are still neglected among pregnant women.[1] IPIs are associated with adverse outcomes, as they might disrupt pregnancy at the maternal-foetal-placental level and impact maternal and neonatal outcomes.[2,3] Despite the potentially enormous at-risk population with IPIs in sub-Saharan Africa (SSA) countries, there is still an important gap in knowledge regarding the pregnancy-related burden of complications that are experienced by women and their offspring.[1,4]

The most frequently reported maternal adverse outcomes associated with IPIs are anaemia and poor pregnancy weight, while neonatal adverse birth outcomes (ABOs) are low-birth-weight, preterm birth and stillbirth.[1,5] Moreover, maternal infection might alter the health and immunity of the infant by transferring parasitic antigens and immune effector molecules, mainly antibodies and cytokines, *in utero* and during lactation.[6] Even today, despite acknowledging that IPIs leave a long-lasting immunological footprint on their hosts, the understanding of which immune mechanisms are altered and how they are changed is limited.[6-8] Some authors reported that babies from IPIs infected mothers can have altered defence against infections, altered response to vaccination and modified risk for allergy and eczema.[6, 8]

In addition, a causal association remains to be completely proven for the adverse birth outcomes associated with IPIs during pregnancy described in some studies.[9-14] Methodological flaws and heterogeneity between study populations could have interfered with the observed complications found in those studies.[15-17] As an example, most have not used multivariate statistics to split the effects of different intestinal parasite species or other contributing factors.[16] Additionally, most pregnant women from these studies conducted mostly in under-resourced countries, were frequently undernourished, also having other major confounders such as HIV infection, malaria and/or sickle cell anaemia. [16] Therefore, there is still a paucity of data that enables to determine whether the adverse outcomes associated with IPIs reported in the literature are due to confounders, differ with different intestinal parasites or with different causes of maternal anaemia.[16]

On the other hand, there is sufficient evidence to suggest that some intestinal parasites are more harmful than others.[1,5,16] For instance, in most cases, long-term helminthic infections are asymptomatic with increased immune Th2 and regulatory responses, suggesting that the helminth has immunomodulatory mechanisms ensuring their survival and chronic existence in the host.[6] Interestingly, those immunological changes associated with helminthic infections resemble those occurring during a successful pregnancy.[6] In addition, only some parasites have a direct role in causing complications such as maternal anaemia, namely, through blood loss, specifically, hookworms, whipworms, and schistosomes.[18-21] In contrast, roundworms or *Ascaris lumbricoides* have an indirect effect, as they interfere with the utilisation of vitamin A, which is required for haematopoiesis.[11, 22] Infection with *A. lumbricoides* is known to be mainly asymptomatic, but in high-burden infections, abdominal pain, pulmonary symptoms, and anaemia may surge.[2] Biliary obstruction associated with *A. lumbricoides* infection has been reported to occur in pregnant women due to a rise in progesterone levels that relaxes the motility of the sphincter-of-Oddi.[2] *A. lumbricoides* has also been linked to postpartum haemorrhage related to ascaris coagulopathic properties with increased clotting and partial thromboplastin time.[2] Then again, the shared immunomodulating mechanisms and the alterations in the host´s immune response during infection by roundworms might also play a protective role during pregnancy.[6]

Regarding human schistosomiasis by trematode worms of the genus *Schistosoma*, the acute infection is usually subclinical, causing mild anaemia. [23, 24] In contrast, chronic infection, might trigger an aggressive immune response that can cause granuloma formation and a fibrotic tissue response with complications.[23-26] The placenta-foetus mechanisms of schistosomiasis have also been reported to lead to ABOs, such as low-birth-weight, prematurity, and stillbirth.[2, 27]

Approximately 90% of *Entamoeba histolytica* infections are asymptomatic or self-limiting.[28-30] Rarely, protozoan-trophozoites, can invade some tissues of the human host with invasive amoebiasis.[28-30] Complications of invasive amoebiasis can range from amoebic dysentery to extraintestinal disease with amoebic-liver-abscesses.[28-30] Alternatively, pregnancy can be a predisposing factor in the reactivation of amoebic infection since the presence of a foetus involves an altered immunological response. [30]

Therefore, parasite - direct or indirect - mechanisms (placental inflammation, maternal iron deficiency, and release of proinflammatory cytokines), can lead to a spectrum of maternal-

placental-foetal effects depending mainly on the type of species, the timing of infection and the intensity of infection, as well as coinfection with multiple parasites and maternal comorbidities.[1, 27, 31-33]

All the above considerations lead us to question what the impact of IPIs among pregnant women and their offspring is, in a specific setting, the smallest Central Africa country - Sao Tome & Principe - known to be an endemic country for four NTDs, namely, soil-transmitted helminths, schistosomiasis (only *S. intercalatum*), lymphatic filariasis and leprosy.[34] Currently, the county´s government is committed to achieving NTD control and elimination as a public health problem by 2025 and has developed a Strategic Plan for the Fight Against NTDs 2019-2025.[34, 35] Additionally, there is an ongoing mass drug preventive chemotherapy administration using a triple drug combination of ivermectin, diethylcarbamazine and albendazole for the elimination programme of *Lymphatic filariasis*.[35] As this programme includes albendazole, which is effective in treating helminthic infections, an additional reduction in the prevalence of helminthic infections is expected in future years. [12, 35] However, IPIs in this setting have only been studied among toddlers, preschool children, and school children, missing out on pregnant women and their unborn babies.[36-38]

Thus, the authors previously conducted the first study in the country regarding this topic and found a high-IPI overall prevalence of 58.2% (95% CI: 52.9-63.3) among pregnant women, mainly due to roundworm *A. lumbricoides* infection (90.9%), followed by *S. intercalatum* (5.2%) and *Entamoeba species* (3.3%).[39] *S. intercalatum* terminology will be used since the reports and diagnoses registered in each woman´s ANC pregnancy card are for *S. intercalatum*. However, *Schistosoma guineensis* seems to reflect the current molecular terminology for this parasite species in this setting as recently published, without any differences in the clinical manifestations or transmission previously documented.[35]

Additionally, a broader project on neonatal and maternal health has been conducted by the authors, studying the causes and factors associated with perinatal and neonatal mortality and morbidity in Sao Tome & Principe.[40-44]

Therefore, in this study the authors go further on from the previous study, filling this gap in knowledge concerning the impact of IPIs among pregnant women and their newborns. Thus, the

participants for the current study were recruited from the same pool as the previous study conducted by the authors.[39] We now aimed to analyse ABOs in accordance with IPI status and according to the types of parasite species, such as helminths, *S. intercalatum* and *Entamoeba sp.*

Moreover, it should be noted that schistosomiasis among pregnant women, globally, has been poorly understood or investigated.[21, 45] To our knowledge, this is the first analysis of *S. intercalatum* infection reports of outcomes in pregnant women and their offspring.

Materials and methods

Study design and period

A hospital-based cross-sectional analytical study was carried out on maternal-neonatal dyads from pregnant women admitted to the Hospital Dr. Ayres de Menezes (HAM) Maternity Unit for delivery, between July 2016 and November 2018.[39]

Setting

The archipelago has approximately 219 161 inhabitants.[46] The level of poverty is high, with 47% of the population practising open defecation and 69.8% having access to clean and safe drinking water.[46] This study was conducted at the HAM maternity unit, situated in the capital city, which also receives deliveries from nearby communities and referral cases from other health care facilities as it is the only hospital in the country. Approximately 82.4% of all deliveries in the country are performed in this hospital.[46]

The IPI prevalence among pregnant women, characterization of antenatal care (ANC) copro-parasitological test results and species found, anthelmintics prescribed for IPIs among pregnant women during ANC and factors associated with IPIs in pregnancy were already analysed and reported in another article.[39]

Participants

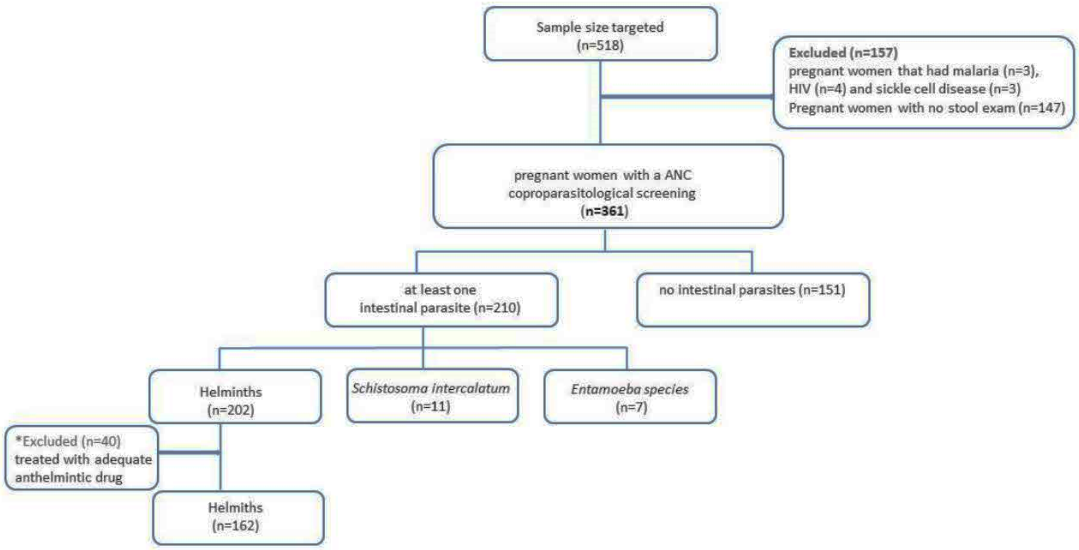
The participants for the current study were recruited from the same pool as the previous study we conducted.[39] The same inclusion criteria were applied. However, the current study had additional exclusion criteria, as pregnant women who received adequate anthelminthic treatment for helminthic infection during the pregnancy period were excluded from the ABO analysis.

Eligibility criteria: All women admitted to the hospital for delivery with a gestational age of 28 weeks or more who underwent a copro-parasitological test during the pregnancy period were eligible to be enrolled.[39] Those who gave birth outside the hospital but were admitted because of postnatal complications in the first 12 hours of life were also included in the study.[39]

Pregnant women with HIV, sickle cell disorder, malaria and who received anthelminthic treatment during pregnancy were excluded for possible confounding causes of maternal anaemia and birth outcomes.[39]

The current study expands upon the previous one by including additional measures related to specific aspects being examined, namely the occurrence of adverse birth outcomes. Pregnant women with an IPI were compared to noninfected women (no-IPI group) according to the IPI species findings of a previous study.[39] Subgroup analyses for ABOs were conducted comparing noninfected women with *i*) monoparasitic-IPI, *ii*) polyparastic-IPI, *iii*) helminths, i*v*) *S. intercalatum*, and *v*) *Entamoeba sp.*_A flowchart of participation in the study is shown in Figure 1.

Figure 1 Flowchart of participation in the study



Note: Combined-group for helminths: 191 (90.9%) *roundworms*, 29 (13.8%) *whipworms*, 3 (1.4%) *hookworms* and 1 (0.5%) *Strongyloides stercoralis*. Pregnant women with polyparasitic infections were included.

*Only for the adverse maternal and perinatal outcome analysis.

Abbreviations: ANC antenatal care; HIV Human Immunodeficiency Virus

Sample size determination and sampling procedures

The sample size for the initial study followed the WHO-steps approach, applying a web-based sample size calculator, Raosoft, and was supported by PASS software, which suggested a minimum sample size of S = 355.[47-49] A total of 518 participants were initially enrolled based on the following assumptions: two-sided 95% confidence level, power of 80% to detect an odds ratio of at least 2 for adverse birth outcomes.[39] A power analysis was additionally performed, varying from 80% to 87% for outcomes such as having maternal anaemia.[39]

Participants were selected through random sampling, from the pile of mothers´ medical admission folders.[39] Women were invited to participate in the study after admission but were interviewed only after they completely recovered from the baby´s delivery.[39]

Data collection tools, procedures, and quality control

Data were collected by a pretested, structured interviewer-administered questionnaire developed from the Sao Tome & Principe Demographic and Health Survey (DHS) and similar studies.[28, 37] Additionally, a standard abstraction checklist from ANC pregnancy cards and newborn records was conducted. The ANC pregnancy card was used to collect information from the participants, regarding copro-parasitological results, treatments, and haemoglobin levels. We also used secondary neonatal clinical data, which were prospectively abstracted from newborns' medical records, regarding low-birth-weight, prematurity, and stillbirth data.

The questionnaires were checked for completeness and consistency. Data collection was regularly reviewed by the supervisors. The principal investigator (a pediatrician) executed and was responsible for the field activities as follows: 1) obtaining consent and enrollment of the mothers, 2) data collection from ANC cards plus maternal and newborn records, 3) newborns' clinical exams (for diagnosis confirmation), 4) face-to-face interviews, and 5) entry of all data collection into the app survey tool. Finally, double data entry was performed to minimize errors during data entry.

Operational definition of variables

In this study, prematurity was defined as birth occurring at less than 37 weeks of gestation.[50] Gestational age at birth was calculated from the first day of the woman's last menstrual period and

counted in completed weeks.[51, 52] Low-birth-weight was defined as an infant born with a weight of less than 2500 grams.[51] Stillbirth was defined, according to the WHO/ICD for International comparison and reporting, as a baby born without any signs of life at or after 28 weeks of gestation or at least 1000 g in birth weight.[52] Maternal anaemia was defined as a haemoglobin concentration <11 g/dl.[53]

The exposure variables in this study included the parasites identified among the 361 copro-parasitological tests performed among pregnant women during ANC recorded in our previous study.[39] A total of 210 copro-parasitological tests were positive.[39] Helminthiasis or combined-group added to a total of 202 monoparasitic infections: 191 (90.9%) roundworm, 29 (13.8%) whipworm, 3 (1.4%) hookworm, 1 (0.5%) *Strongyloides stercoralis*.[39] *Schistosoma intercalatum* infection was found in 11 pregnant women and *Entamoeba sp.* was found in 7 women.[39] Cases of polyparasitism, defined as the presence of two or more parasite species in the same host, were found in 25 (11.9%) pregnant women.[39]

Data management and statistical analyses

Data were entered into the QuickTapSurvey (2010-2021 Formstack) offline app survey tool. Data entry for this study into the app survey was first cleaned by creating a data entry field in Excel, and all categorical responses were checked for completeness and accuracy and to eliminate errors and inconsistent data. Data were further analysed using the Statistical Package for the Social Sciences for Windows, version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Data analysis in this study was carried out in two stages. The first stage involved pooling data for descriptive statistics with categorical variables presented as frequencies and percentages and quantitative variables presented as the mean and standard deviation, as appropriate. For the ABO analysis, pregnant women with an IPI (n=210) were divided according to the presence of one or more parasites in the copro-parasitological test and the specific type of parasite. Subgroup analyses for ABOs were conducted comparing the no-IPI or noninfected women group (n=151) with *i*) monoparasitic-IPI (n=145), *ii*) polyparastic-IPI (n=25), *iii*) helminths (n=162), *iv*) *S. intercalatum* (n=11), and *v*) *Entamoeba sp.* (n=7). This second stage involved the use of the nonparametric chi-square test and Fisher's exact test, as appropriate. A level of significance of α=0.05 was considered.

Ethics approval and consent to participate

This study was approved by dedicated ethics oversight bodies, namely the Ministry of Health of Sao Tome & Principe and the main board of the Hospital Dr. Ayres de Menezes. The study complies with the Declaration of Helsinki. Written informed consent was obtained from all participants after the purpose of the research was explained orally by the researcher. Approval by the participants´ parents or legal guardians was obtained in the case of adolescents under 16 years of age or for illiterate women.

Results

Characteristics of the study participants

Of the 361 pregnant women included, 233 (64.5%) were aged 20 to 34, and the mean age was 26.96 ±7.0 years (minimum age 14 and maximum 43 years). Three hundred and three (85.4%) participants were married, 196 (54.3%) ended school with a primary level of education, and 12 (3.3%) were illiterate. Unemployment was identified in 250 (69.6%) women. Table 1 shows the sociodemographic characteristics of the participants.

Pregnancy-related characteristics: A parity of one to four was observed in 227 (62.9%) pregnant women, with 103 (28.5%) of the participants being nulliparous and 31 (8.6%) grand multiparous. Complete ANC service utilization with ANC 8+ contacts was achieved by 169 (46.8%) pregnant women, while 24 (6.6%) had fewer than 4 ANC contacts.

Community-level feature: residency in a rural area was assessed for 192 (53.6%) participants. Access to improved water sources was reported for 304 (84.2%) pregnant women, and 156 (43.6%) practiced open defecation.

Table 1 Sociodemographic, pregnancy-related and community-level characteristics of the participants

Variables	Frequency (n=361)	Percentage (%)
Age		
14-19	65	18
20-34	233	64.5
≥35	63	17.5
Education		
none	12	3.3
primary	196	54.3
secondary	126	34.9
higher	27	7.5
Employment		
not working	250	69.6
working	109	30.4
Marital status		
union/married	303	85.4
single	52	14.6
Baby´s father education		
none	8	3.3
primary	116	47.3
secondary	94	38.4
higher	27	11
Residence		
urban	166	46.4
rural	192	53.6
Water source		
improved water	304	84.2
no	57	15.8
Household sanitation		
with sanitation	202	56.4
open defecation	156	43.6
Parity		
0	103	28.5
1-4	227	62.9
5+	31	8.6
ANC visits		
< 4	24	6.6
4-7	168	46.5
≥ 8	169	46.8

Abbreviations: ANC: antenatal care

Adverse outcomes

Of the 361 participants, maternal anaemia was identified in 127 (39.6%) pregnant women. Child-related ABOs were found in 82 (23%) newborns, as follows: 26 (8.1%) premature, 48 (14.9%) low-birth-weight and 8 (2.5%) stillbirths (Table 2).

Table 2 Adverse outcomes observed among the participants (n=321)

Variables	Frequency (n=321)*	Percentage (%)
Maternal anaemia		
yes	127	39.6
no	194	60.4
Prematurity		
yes	26	8.1
no	295	91.9
Low-birth-weight		
yes	48	14.9
no	273	85.1
Stillbirth		
yes	8	2.5
no	313	97.5

*Forty women who received adequate anthelmintic treatment (albendazole, mebendazole or piperazine) for helminthic infection during pregnancy were excluded.

Abbreviations: IPI - intestinal parasitic infection

Association between ABOs and IPIs in pregnant women

ABOs were compared between pregnant women with monoparasitic-IPI (n=145) and noninfected women (n=151), as described in Table 3. Maternal anaemia was found in 46.7% and 38.7% of pregnant women in the monoparasitic-IPI and no-IPI groups, respectively. A statistically significant difference was not found between groups for maternal anaemia. Regarding offspring features, ABOs in the monoparasitic-IPI group compared to the no-IPI group, namely, prematurity (6.2% vs 10.9%), low-birth-weight (11% vs 19.2%) and stillbirths (3.4% vs 1.3%), had no statistically significant difference.

Table 3 Adverse outcomes in pregnant women with a monoparasitic-IPI compared to the noninfected group

	monoparasitic- IPI (n=145) n (%)	no-IPI (n=151) n (%)	p value
Maternal anaemia			0.182
yes	63 (46.7)	55 (38.7)	
no	72 (53.3)	87 (61.3)	
Prematurity			0.175
yes	9 (6.2)	16 (10.6)	
no	136 (93.8)	135 (89.4)	
Low-birth-weight			0.070*
yes	16 (11)	29 (19.2)	
no	129 (89)	122 (80.8)	
Stillbirth			0.275*
yes	5 (3.4)	2 (1.3)	
no	140 (96.6)	149 (49)	

*Fisher´s exact test

Abbreviations: IPI - intestinal parasitic infection

ABOs between pregnant women with polyparasitic-IPI (n=25) and noninfected pregnant women (n=151), described in Table 4, also had no statistically significant difference.

Table 4 Adverse outcomes in pregnant women with a polyparasitic-IPI compared to the noninfected group

	Polyparasitic-IPI (n=25) n (%)	no-IPI (n=151) n (%)	*p* value
Maternal anaemia			
yes	9 (36)	55 (38.7)	0.796
no	16 (64)	87 (61.3)	
Prematurity			
yes	1 (4)	16 (10.6)	0.473*
no	24 (96)	135 (89.4)	
Low-birth-weight			
yes	3 (12)	29 (19.2)	0.576*
no	22 (88)	122 (80.8)	
Stillbirth			
yes	1 (4)	2 (1.3)	0.370*
no	24 (96)	149 (49)	

*Fisher´s exact test

Abbreviations: IPI - intestinal parasitic infection

Soil-Transmitted Helminths

The 162 untreated pregnant women with a helminthic infection had the following ABOs: 45.8% maternal anaemia, 6.2% prematurity, 11.7% low-birth-weight and 3.7% stillbirth rate (Table 5). No statistically significant difference was found for ABOs between women infected with helminthic infection and noninfected women. The low-birth-weight comparison between the helminth subgroup (11.7%) and the noninfected group (19.2%) had a p value=0.067.

Table 5 Adverse outcomes in pregnant women with a helminthic infection compared to the noninfected group

	Helminths[1] (n=162) n (%)	no-IPI (n=151) n (%)	p value
Maternal anaemia			0.223
yes	70 (45.8)	55 (38.7)	
no	83 (54.2)	87 (61.3)	
Prematurity			0.157
yes	10 (6.2)	16 (10.6)	
no	152 (93.8)	135 (89.4)	
Low-birth-weight			0.067
yes	19 (11.7)	29 (19.2)	
no	143 (88.3)	122 (80.8)	
Stillbirth			0.285*
yes	6 (3.7)	2 (1.3)	
no	156 (96.3)	149 (98.7)	

*Fisher´s exact test

[1]For helminth-related adverse outcomes, 40 women who received adequate anthelmintic treatment (albendazole, mebendazole or piperazine) during pregnancy were excluded from this ABO analysis.

Abbreviations: IPI - intestinal parasitic infection

Schistosoma intercalatum

Out of the eleven pregnant women with a *S. intercalatum*-positive copro-parasitological test, one low-birth-weight baby was identified, and no preterm baby or stillbirth outcomes were found (Table 6). Maternal anaemia was found in 36.4% and 38.7% of pregnant women with a *S.*

intercalatum-IPI and noninfected women, respectively. No statistically significant difference was found for low-birth-weight and maternal anaemia between the two groups.

Table 6 Adverse outcomes in pregnant women with a *S. intercalatum* positive copro-parasitological result compared to the noninfected group

	S. Intercalatum (n=11) n (%)	no-IPI (n=151) n (%)	*p* value
Maternal anaemia			
yes	4 (36.4)	55 (38.7)	1.000*
no	7 (63.6)	87 (61.3)	
Prematurity			
yes	0	16 (10.6)	0.603*
no	11 (100)	135 (89.4)	
Low-birth-weight			
yes	1 (9.1)	29 (19.2)	0.691*
no	10 (90.9)	122 (80.8)	
Stillbirth			
yes	0	2 (1.3)	1.000*
no	11 (100)	149 (98.7)	

*Fisher´s exact test

Abbreviations: IPI - intestinal parasitic infection

Entamoeba species

All seven pregnant women with an *Entamoeba sp.*-positive copro-parasitological test had no preterm baby, low-birth-weight or stillborn offspring (Table 7). Maternal anaemia was found in 16.7% and 38.7% of women with *Entamoeba sp*-IPI and noninfected women, respectively. No statistically significant difference was found for maternal anaemia between women with *Entamoeba sp.* and noninfected women.

Table 7 Adverse outcomes in pregnant women with an *Entamoeba species*-positive copro-parasitological result compared to the noninfected group

	E histolytica (n=7) n (%)	no-IPI (n=151) n (%)	*p* value
Maternal anaemia			
yes	1 (16.7)	55 (38.7)	0.409*
no	5 (83.3)	87 (61.3)	
Prematurity			
yes	0	16 (10.6)	1.000*
no	7 (100)	135 (89.4)	
Low-birth-weight			
yes	0	29 (19.2)	0.351*
no	7 (100)	122 (80.8)	
Stillbirth			
yes	0	2 (1.3)	1.000*
no	7 (100)	149 (98.7)	

*Fisher´s exact test

Abbreviations: IPI - intestinal parasitic infection

Discussion

Women living in endemic countries are known to have a higher risk of acquiring an IPI during their pregnancy and consequently to suffer eventual complications from these NTDs.[2, 9-14] Thus, this study was conducted to clarify the adverse outcomes among these IPI-infected pregnant women and their offspring in Sao Tome & Principe.

Overall, approximately 40% of women in this study were anaemic, similar to the prevalence of 46% anaemia among pregnant women in SSA countries and lower than the 61% rate published for the country.[46, 53] Confounders for adverse outcomes, namely HIV infection, sickle cell disorder, and malaria were excluded from this analysis. Nonetheless, although IPIs are reported to cause or aggravate maternal anaemia through multiple mechanisms, a statistically significant difference was not found when each infected subgroup was compared to the noninfected counterpart, highlighting that anaemia in this setting is mainly multifactorial.[5]

Approximately one-quarter of the newborns had child-related adverse outcomes, mostly due to low-birth-weight. When child-related ABOs were compared between IPI subgroups and their noninfected counterparts, no statistically significant difference was found between the groups. However, it should be acknowledged that an almost significant statistically significant difference (p value=0.067) was found, suggesting that pregnant women with a helminthic infection had fewer low-birth-weight babies than noninfected mothers. This is in accordance with some studies of helminths alone that have found no association between infection and birthweight.[16, 54-55] Fairley et al. found that pregnant women with helminthic infections have higher birth weights even in the presence of coinfections.[55] Thus, it can be speculated that helminthic infection can promote an immunological environment surrounding the uterus into a more advantageous milieu, which can contribute to enhanced foetal weight gain, although more studies are needed to clarify this.[6]

In our study, factors such as the parasitic infection intensity and the timing of infection (before pregnancy or in which trimester), were not available, missing out on major clues that could explain or support our findings.[18, 56-58] However, the main factor supporting our findings is the type of parasite infecting the participants of this study and its respective pathogenesis mechanisms.[1] As previously mentioned, the most predominant parasite in this study was the roundworm *A. lumbricoides* (90.9%), which is known to be mainly an asymptomatic infection.[2, 39] This lack of

association between *A. lumbricoides* infection and adverse outcomes, such as maternal anaemia, prematurity and stillbirths, was also reported in other studies conducted in SSA countries, namely, in Kenya and in Tanzania.[9, 10] In contrast, Rodríguez-Morales et al. in Venezuela reported that *A. lumbricoides* infection represented a twofold risk for anaemia at pregnancy, similar to Demeke G et al. found in Ethiopia.[14, 57]

Regarding schistosomiasis during pregnancy, as previously mentioned, there is a paucity of studies. To the best of our knowledge, this is the first report on *S. intercalatum* during pregnancy.[39] Of the eleven pregnant women with a positive *S. intercalatum* copro-parasitological test, only four women had maternal anaemia, and one newborn had low-birth-weight. The lack of adverse outcomes with this parasite can rely on the fact that *S. intercalatum* infections are known to be asymptomatic or to be associated with a dysenteric syndrome with bloody stools without further complications.[24, 25, 45, 59] Moreover, intestinal schistosomiasis due to *S. intercalatum* is typically characterized by a low location of the lesions at the level of the rectum and sigmoid colon and relatively minor liver pathology without portal hypertension.[24, 25, 59] The current national preventive chemotherapy programme with praziquantel for schistosomiasis control only targets school children, missing out on other at-risk populations.[35, 39] Therefore, our findings also have some policy implications since the 2017 Sao Tome & Principe national survey suggested the elimination of *S. intercalatum* among children, claiming to be one of the first countries to eliminate schistosomiasis.[35] Thus, according to our research, *S. intercalatum* is still a reality among pregnant women in the country; thus, women-of-reproductive age should be included in the country´s preventive chemotherapy programmes to achieve the goal of eliminating schistosomiasis in the country.[23]

Entamoeba sp. is a rare NTD, and none of our seven pregnant women enrolled with a copro-parasitological test positive for *Entamoeba sp.* had any child-related adverse outcomes, and only one mother had anaemia. This finding is contrary to the Mahande study, which reported twofold increased odds of preterm delivery among women with *Entamoeba* infection compared with noninfected women, probably due to penetration of the intestinal mucosa and placental barrier by *E. histolytica*.[10] Amebiasis is reported to be more severe in pregnant women than in nonpregnant women, linked to the reduced production of IgA during pregnancy, which may lead to subchronic inflammation and placental dysfunction resulting in preeclampsia, preterm delivery, and foetal growth restriction.[29, 30] None of the drugs used in the country for preventive chemotherapy

programmes have efficacy in treating *Entamoeba* infections.[30, 35] Thus, routine ANC screening for IPIs through copro-parasitological exams should be maintained, and pregnant women should receive adequate follow-up.[30, 39]

Overall, this study is a useful starting point that can assist Sao Tome & Principe policy makers in understanding the impact of IPIs among pregnant women and in rethinking the targets for preventive chemotherapy programmes, including women-of-reproductive age, as previously mentioned for schistosomiasis.

Nonetheless, primarily, what this study brings, is the opportunity to discuss what are the real benefits and risks of providing anthelmintic treatment during pregnancy for this specific setting, facing the lack of adverse outcomes associated with roundworms infections.

As recently highlighted by some authors, there may be unexpected consequences of IPI treatment, as maternal infections can affect the priming of infant immune systems, with potential effects on children later in life.[16, 22] Additionally, questions remain regarding the efficacy of anthelmintic treatment reported in some studies. [16, 22] For instance, efficacy can be linked to cases with very high parasite burdens, dietary insufficiencies or both and that pregnant women adequately nourished, without comorbidities and with moderate or low parasite burden, may not benefit from anthelmintic treatment.[16, 22] On the other hand, anthelmintic treatment during pregnancy has been associated with an increased incidence of eczema in children, suggesting that anthelmintics may affect the development of mechanisms regulating child immune responses.[7, 16, 60] In addition, anthelmintic treatment may also have additional risks by altering maternal blood glucose regulation, microbiota, or hormonal environment.[16] Therefore, some caution to promote broad efforts to treat all pregnant women during pregnancy is warranted until future studies clarify the real impact and outcomes and how they play out under different ecological conditions.[16]

Therefore, treating infected pregnant women is far from straightforward, and the debate is whether helminthic infections are "old enemies or old friends", especially during pregnancy.[16, 22]

Recent studies focused on the benefits of helminthic infections. Some authors argue that immune regulation by parasites, mainly the host immune response to roundworms, can increase fertility rates in infected women.[6] Moreover, in endemic countries, mainly for *Ascaris lumbricoides* or roundworms, the burden of infection has been associated with lower frequencies of allergic symptoms and skin test positivity.[6]

Therefore, if in our previously published study, we recommended that all the "treatment missing opportunities" identified among pregnant women with an IPI in Sao Tome & Principe be urgently addressed, we now consider that there are more benefits in postponing anthelmintic treatment in all asymptomatic and healthy pregnant women with a helminthic infection after the baby´s delivery.[39]

Strengths and limitations

This is a cross-sectional study that provides a useful contribution in exploring the relationship between parasitic infections during pregnancy and adverse outcomes. Moreover, major confounders, such as HIV infection, malaria, sickle cell anaemia and anthelmintic treatment were excluded. Both groups (IPI and no-IPI) had almost the same number of participants with a sample that allowed characterization and adverse outcomes analysis.

On the other hand, an important limitation is the negligible number of participants with *S. intercalatum* and *Entamoeba sp.* found in the study. Thus, future studies with larger samples will be needed to clarify the lack of adverse outcomes associated with these species. Other limitations, commented before, were that information regarding the intensity and timing of the parasitic infection was not available.

Notwithstanding the abovementioned limitations, the present study adds to the narrow literature available on IPIs during pregnancy and associated complications. Moreover, this study represents a first step in the description of ABOs among pregnant women and their offspring in this high-IPI endemic resource-constrained setting.

Future studies

Larger studies are needed to better understand these host–parasite interactions and the overall impact and role of intestinal parasites among pregnant women and their offspring. Additionally, since helminthic infections are known to affect blood glucose, insulin resistance and diabetes, linking it to improvement of glucose tolerance and lower blood levels, it should be important to include the association with gestational diabetes and IPI in future studies.[16] Preeclampsia associations with intestinal parasites should also be included in future studies, since immunological effects of helminths on maternal immunity, by increasing maternal tolerance of the foetus and by moderating inflammatory responses, are believed to have a protective role from preeclampsia.[16]

Conclusions

We were unable to find any statistically significant difference in maternal anaemia, prematurity, low-birth-weight, or stillbirth that could be associated with intestinal parasitic infections during pregnancy. Helminthic-infected pregnant women tended to have fewer low-birth-weight babies in comparison with noninfected ones, although a statistically significant difference was not established. Moreover, roundworms were the main species infecting pregnant women in this study, supporting this absence of complications in pregnant women and in their offspring. Thus, these findings suggest that in this setting, the treatment of an IPI during pregnancy should be postponed for all pregnant women who are asymptomatic and without comorbidities. Hence, the decision to treat should be based on the type and impact of the intestinal parasite on the pregnant-foetus on an individual-basis.

Declarations

Ethics approval and consent to participate

This study was approved by dedicated ethics oversight bodies, namely the Ministry of Health of Sao Tome & Principe and the main board of the Hospital Dr. Ayres de Menezes. The study complies with the Declaration of Helsinki. Written informed consent was obtained from all participants after the purpose of the research was explained orally by the researcher. Approval by the participants´ parents or legal guardians was obtained in the case of adolescents under 16 years of age or for illiterate women.

Availability of data and materials

All data generated or analysed during this study are included in this paper or in the published article.[39]

Competing interests

The authors declare that they have no financial or nofinancial competing interests.

Consent for publication

Not applicable.

Authors' contributions

AV, MCM, and FP performed the conception and design of the study. AV was responsible for field activities, data collection, and writing the manuscript. MCM and FP critically evaluated and made progressive suggestions throughout the study and revised the manuscript. MA and ALP performed the statistical analysis and reviewed the manuscript. SS and NB were involved in the study design at the country level. All the authors read and approved the final draft of the manuscript.

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Abbreviations

HAM: Hospital Dr. Ayres de Menezes; ANC: antenatal care; WHO: World Health Organization; NTD: Neglected Tropical Diseases.

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RESEARCH ARTICLE

Adverse birth outcomes and associated factors among newborns delivered in Sao Tome & Principe: A case–control study

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Abstract

Background

Newborns with one-or-more adverse birth outcomes (ABOs) are at greater risk of mortality or long-term morbidity with health impacts into adulthood. Hence, identifying ABO-associated factors is crucial for devising relevant interventions. For this study, ABOs were defined as prematurity (PTB) for gestational age <37 weeks, low birth weight (LBW) <2.5 kg, macrosomia >4 kg, asphyxia for a 5-minute Apgar score <7, congenital anomalies, and neonatal sepsis. This study aimed to assess factors associated with ABOs among babies delivered at the only hospital of Sao Tome & Principe (STP), a resource-constrained sub-Saharan-Central African country.

Methods

A hospital-based unmatched case–control study was conducted among newborns from randomly selected mothers. Newborns with one-or-more ABO were the cases (ABO group), while healthy newborns were the controls (no-ABO group). Data were collected by a face-to-face interview and abstracted from antenatal care (ANC) pregnancy cards and medical records. Multivariable logistic regression analysis was performed to identify ABO-associated factors considering a level of significance of $\alpha = 0.05$.

Results

A total of 519 newborns (176 with ABO and 343 no-ABO) were enrolled. The mean gestational age and birthweight of cases and controls were 36 (SD = 3.7) weeks with 2659 (SD = 881.44) g and 39.6 (SD = 1.0) weeks with 3256 (SD = 345.83) g, respectively. In the multivariable analysis, twin pregnancy [aOR 4.92, 95% CI 2.25–10.74], prolonged rupture of membranes [aOR 3.43, 95% CI 1.69–6.95], and meconium- fluid [aOR 1.59, 95% CI 0.97–

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2.62] were significantly associated with ABOs. Eight or more ANC contacts were found to be protective [aOR 0.33, 95% CI 0.18–0.60, p<0.001].

Conclusion

Modifiable factors were associated with ABOs in this study and should be considered in cost-effective interventions. The provision of high-quality ANC should be a priority. Twin pregnancies and intrapartum factors such as prolonged rupture of membranes and meconium-stained amniotic fluid are red flags for ABOs that should receive prompt intervention and follow-up.

Introduction

Adverse birth outcomes (ABOs) are a major global public health problem linked to child mortality and morbidity since they can impact children's short- and long-term well-being due to neurological and health problems throughout their life course [1,2]. Inevitably, a newborn with an ABO is at a higher risk for mortality than newborns without an ABO [3]. Additionally, ABOs may disrupt the family condition, leading to high individual and social costs [4].

The magnitude of ABOs worldwide has dramatically decreased in recent decades, although a large gap still exists between high-income and low- and middle-income countries (LMICs), making birth outcomes important measures of health [4]. The specific burden of each ABO can vary according to country specificities, although preterm birth (PTB) is the most well-accepted benchmark for morbidity attributable to early gestation [5]. In recent years, ABOs in LMICs have received attention, with a wide range of ABOs being reported across different studies [6–11]. While some studies include indicators for early gestation, such as PTB, fetal growth restriction, low birth weight (LBW) as well as perinatal mortality and fetal loss/miscarriage [4,5], others exclusively analyze live newborns at birth [12]. Furthermore, ABOs can coexist and share the same underlying risk factors, are mostly multifactorial, physiologically diverse, and not entirely well understood, despite decades of research [5].

Different studies have revealed that diverse risk factors are associated with ABOs [1,4,5,8]. Studies in LMICs have reported numerous sociodemographic factors, maternal characteristics, previous pregnancy outcomes, neonatal factors, and socioeconomic and health system-related factors [8,12,13]. For example, mothers with previous pregnancy outcomes of PTB or LBW are more likely to have recurrence of these ABOs than those without previous PTB or LBW babies [6,9]. A study on maternal health during pregnancy found that women who had at least one comorbidity during their pregnancy had a twofold higher risk of delivering LBW babies than women without any health problems [14]. Indeed, studies report that antepartum infections such as malaria, syphilis and others, and noninfectious conditions such as anemia, hypertension, hyperglycemia, and obstetric complications are all linked to ABOs [9–12]. Additionally, lack of adequate antenatal care (ANC), household air pollution from unclean cooking fuels, open defecation, no access to improved water, violence, and other socioeconomic disparities are also considered important risk factors for ABOs in sub-Saharan African (SSA) countries [15–18].

Sao Tome & Principe (STP) is an SSA country with limited data on the overall ABO rate at the country level, and in the current era of the Sustainable Development Goals (SDGs), neonatal mortality remains high, demanding urgent intervention in ABO reduction [19–21]. As discussed above, most risk factors contributing to ABOs are amenable to modification, although they are not the same across different cultures and socioeconomic statuses within a society

[4,18]. Thus, knowing STP context-specific reality of ABOs enables to target and implement the most proper evidence-based interventions for this setting. For this study, ABOs were defined as PTB, LBW, macrosomia, major congenital anomaly, birth asphyxia and neonatal sepsis suspicion. STP has significant health resource-constraints, since there are no blood cultures or other microbiologic techniques available, and other procedures such as umbilical arterial blood gas analysis, are not feasible [22,23]. Moreover, there are no neonatal intensive care units and, similar to other units in LMICs, lacks a mechanical ventilator or any continuous positive airway pressure machine and surfactant therapy for neonatal care [24,25]. Therefore, birth asphyxia is only determined by using the APGAR score [26–29], and early-onset neonatal sepsis diagnosis is done in a suspicion-based algorithm [24,25].

Thus, this study aimed to improve neonatal health outcomes in this very resource-constrained SSA country by identifying the factors associated with ABOs among newborns delivered at the only hospital maternity unit in STP. Thus, knowledge of the burden of ABOs and key associated factors in this specific setting can be used to design targeted interventions and better allocate resources for effective ABO reduction.

Materials and methods

Study design and period

A facility-based unmatched case–control study was conducted in STP among 519 newborns whose mothers gave birth at Hospital Dr. Ayres de Menezes (HAM) Maternity Unit. The recruitment of newborns' mothers occurred from July 2016 to November 2018.

Setting

The archipelago of STP, the smallest Central SSA country, is a 219 161-inhabitant country, with a young population and an annual birth cohort of approximately 6.521 babies [19]. The rate of deliveries in health units is approximately 98%, with 82.4% occurring at the HAM maternity unit, the only hospital in the country [20]. The HAM is a tertiary healthcare facility and receives complicated cases referred from facilities with lower levels of care, as it is the only facility with Comprehensive Emergency Obstetric Care (CEmOC) capable of providing blood transfusions and performing cesarean sections.

The maternity unit has a resource-constrained unit for small and sick newborn babies—Newborn Care Unit (NCU)—with six baby cots, in which babies receive oxygen through nasal prongs or face masks and are assisted by general doctors and nurses, since there are no neonatologists and only two pediatricians in STP.

Participants

The eligibility criteria for participants were as follows: 1) all neonates delivered at HAM and 2) newborns who were born outside the hospital but were later admitted at HAM on the day of birth. A total of 535 newborns were initially enrolled.

The exclusion criteria included the following: 1) all neonates delivered at HAM born without any signs of life (stillbirths), 2) newborns whose mothers had cognitive impairment, and 3) adolescent or illiterate mothers who had not obtained permission from their parents or legal guardians to participate in the study. Sixteen met the exclusion criteria (stillbirths), with a total of 519 participants enrolled.

Selection of cases and controls

Cases (ABO group) were newborns with at least one adverse birth outcome: PTB, LBW, macrosomia, birth asphyxia, congenital anomaly and/or probable neonatal sepsis (see Operational definition of variables). Controls (no-ABO group) were healthy newborns without adverse birth outcomes ($\geq$ 37 gestational weeks at birth, weight $\geq$ 2.5 kg at birth and not greater than 4 kg, 5-min APGAR score $\geq$ 7, no congenital anomaly, and no probable sepsis).

Sample size determination and sampling procedures

Sample size followed the WHO-steps approach [30] applying a web-based sample size calculator, Raosoft, which suggested a minimum sample size of S = 355, which placed the right dimension between 355 (95%) and 579 (99%) confidence [31]. A total of 535 participants were enrolled based on the following assumptions: two-sided 95% confidence level, and power of 80% to detect an odds ratio of at least 2 for ABOs. This sample size was also supported by PASS software [32].

A random sampling was applied to recruit the newborn's mother, selecting every second interval folder from the pile of mothers´ medical folders, and occurred during daytime hours of working days. The mothers who consented were interviewed after recovery from the delivery, and the mother-newborn dyads were followed-up throughout their stays until hospital discharge.

Data collection tools, procedures, and quality control

Data were collected by a pre-tested, structured interviewer-administered questionnaire developed from the STP Demographic and Health Survey (DHS) and similar studies [18,19,20]. Additionally, a standard abstraction checklist from ANC pregnancy cards and maternal and newborn records was conducted. The questionnaire contains information related to the sociodemographic characteristics of parents, preconception healthcare services and obstetrics-related characteristics of the mothers.

To ensure data quality, pretesting was performed on 10 cases and 13 controls and modified based on the findings, mainly adjusting terminology for more culturally friendly terms. The questionnaires were checked for completeness and consistency. Data collection was regularly reviewed by the supervisors. The principal investigator (a pediatrician) executed and was responsible for the field activities as follows: i) obtaining consent and enrollment of the mothers, ii) data collection from ANC cards plus maternal and newborn records, iii) newborns' clinical exams (for diagnosis confirmation), iv) face-to-face interviews, and v) entry of all data collection into the app survey tool. Finally, double data entry was performed to minimize errors during data entry.

Operational definition of variables

ABOs: 1) preterm was defined as a birth that occurred before 37 completed weeks (less than 259 days) of gestation [33]; 2) LBW as a weight of $<$ 2.5 kg at birth [34,35]; 3) macrosomia as a birth-weight over 4000 g irrespective of gestational age [36]; 4) birth asphyxia as an APGAR score at 5-minutes inferior to seven [26,27]; 5) congenital anomaly as structural changes in one or more parts of the infant's body that are present at birth [16]; and/or 6) probable neonatal sepsis or early-onset neonatal sepsis was defined through a clinical-based algorithm as having one or more of the following: i) newborns with early suspicious signs and symptoms (hypothermia or fever, lethargy, poor perfusion, hypotonia, bulging fontanel, respiratory

distress, apnea, and gasping respiration), ii) with or without an identifiable maternal infectious risk, and/or iii) requiring NCU admission and antibiotic treatment [37,38].

Maternal infectious risk: operationally defined as i) maternal fever (axillary temperature >37.9 C) at the time of delivery, and/or ii) prolonged rupture of membranes (PROM) (≥18 hours) [34], and/or iii) meconium or foul-smelling amniotic fluid [39].

Gestational age: estimated from the date of onset of the last normal menstrual period or through ultrasound dating of pregnancy [12,40].

Maternal anemia: hemoglobin concentration <11 g/dl.

Intrapartum conditions: included fetal malpresentation [41], umbilical cord complications [42], PROM [37,43], meconium-stained amniotic fluid [44], postpartum hemorrhage (>500 mL bleeding), preeclampsia (hypertension ≥140/90 mmHg and proteinuria in women who were normotensive at ANC), and obstructed labor [45]).

Data analysis

Data were entered into the QuickTapSurvey app (2010–2021 Formstack), an offline survey app tool, and exported to Excel to be further checked for completeness, coded, entered, and cleaned. Data were analyzed using SPSS version 25. In this study, cases were coded as 1, and controls were coded as 0 for analysis. The proportion of missing data ranged from 0.8 to 10% across variables. Missing values higher than 10% were described in the analysis.

Descriptive statistics were used to describe the frequency distribution of each of the variables mentioned earlier. The chi-square test was used to compare the proportion of cases and controls between selected categorical variables. To identify factors associated with ABO, univariable and multivariable logistic regression analyses were performed. In the univariable analysis, explanatory variables with a p value <0.25 were candidates for a multivariable logistic regression model to monitor the influence of confounding variables. With their 95% confidence intervals (95% CI), crude (cOR) and adjusted (aOR) odds ratios were determined to assess the strength and existence of an association. The level of significance $\alpha = 0.05$ was considered.

Ethics approval and consent to participate

The study complies with the Declaration of Helsinki and was approved and consented to by dedicated ethics oversight bodies such as the Ministry of Health of STP and by the main board of HAM, since at the time the study protocol was submitted, there was no ethics committee in STP. All methods in our study were performed in accordance with the relevant guidelines and regulations in practice. Written informed consent was obtained from all participants after the purpose of the research was explained orally by the researcher. Approval by the participants' parents or legal guardians was asked in the case of adolescents under 16 years of age or for illiterate women. The participants or their legal representatives also consented to have the results of this research work published. Participation in the survey was voluntary, as participants could decline to participate at any time during the study.

Results

A total of 519 newborns (176 cases and 343 controls) were enrolled. The newborn's mean gestational age (GA) was 38.73 weeks with a standard deviation (SD) of 2.62 (minimum 25—maximum 43 weeks). The mean birth weight was 3053.79 ±(SD = 649) g (minimum 900 g–maximum 4650 g). Cases had a mean GA and birth weight of 36.02 ±(SD = 3.7) and 2659.66 ±(SD = 881.44) g, respectively, while their counterparts had 39.61 ±(SD = 1.03) weeks and 3256.02 ±(SD = 345.83) g, respectively. The mean maternal age was 26.5 years with a standard

deviation of 7.03 (minimum 14—maximum 43 years old). The mean maternal age for cases and controls was 26.99 (SD = ±7.15) and 26.24 (SD = ±6.96), respectively.

Adverse birth outcomes

The current study revealed that 343 (66%) births were healthy live births, while the remaining 176 (34%) were births with child-related adverse birth outcomes. Regarding ABOs (Table 1), 92 (17.7%) were PTB, 83 (16%) had LBW, and 42 (8.1%) had birth asphyxia. Eight babies (1.5%) had congenital anomalies, 21 (4%) had a probable neonatal sepsis and 21 (4%) had a birth weight higher than four kilograms (macrosomia).

The maternal characteristics as well as antepartum, intrapartum, and postpartum factors for all participants and for cases versus controls are described in Table 2.

Factors associated with adverse birth outcomes

In the univariable logistic regression, number of ANC contacts, twin pregnancy, delivery assisted by midwives or obstetricians, preeclampsia, PROM, obstructed labor, cesarean section, meconium-stained amniotic fluid, and infectious risk were eligible for multivariable analysis (Table 3).

In the multivariable logistic analysis, twin pregnancy (aOR 4.92, 95% CI 2.25–10.74; $p<0.001$), PROM (aOR 3.43, 95% CI 1.69–6.95, $p = 0.001$), and meconium-stained amniotic fluid (aOR 1.59, 95% CI 0.97–2.62, $p = 0.068$) were independently significantly associated with ABOs (Table 3). Having 8 or more ANC contacts was found to be a protective factor (aOR 0.33, 95% CI 0.18–0.60, $p<0.001$), as shown in Table 3.

Discussion

Assessing neonatal ABOs and identifying contributing factors can help avoid neonatal mortality and morbidity thoroughly and thoughtfully. As a result, the goal of this study was to identify the factors related to ABOs in neonates admitted at birth to HAM in the capital city of

Table 1. Frequency and types of adverse birth outcomes related to the newborns among deliveries attended in Hospital Dr. Ayres de Menezes, Sao Tome & Principe.

Adverse birth outcomes		Frequency	Percent
Preterm baby or birth	No	427	82.3
	Yes	92	17.7
Low Birth Weight	No	436	84
	Yes	83	16
Macrosomia	No	498	96.0
	Yes	21	4.0
Congenital anomaly	No	511	98.5
	Yes	8	1.5
Birth asphyxia	No	477	91.9
	Yes	42	8.1
Probable neonatal sepsis	No	498	95.9
	Yes	21	4.0
ABOs observed in a new birth	no ABO	343	66
	at least 1 ABO	176	34
	Total	519	100.0

Abbreviations: ABOs—adverse birth outcomes.

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Table 2. Maternal characteristics, antepartum, intrapartum, and postpartum factors for all participants and for cases (newborns with ABO) versus controls (newborns with no-ABO).

Variables	TOTAL n = 519 (%)	ABO n = 176 n (%)	no-ABO n = 343 n (%)	*p*-value
Sociodemographic factors				
Age				0.277
14–16	29 (5.6)	11 (6.3)	18 (5.2)	
17–19	74 (14.3)	21 (11.9)	53 (15.5)	
20–34	330 (63.6)	108 (61.4)	222 (64.7)	
≥35	86 (16.6)	36 (20.5)	50 (14.6)	
Maternal education				0.004
none	19 (3.7)	7 (4)	12 (3.5)	
primary	298 (57.4)	111 (63.1)	187 (54.5)	
secondary	166 (32)	40 (22.7)	126 (36.7)	
higher	36 (6.9)	18 (10.2)	18 (5.2)	
Maternal occupation				0.921
housewife	326 (62.8)	111 (63.1)	215 (62.7)	
student	36 (6.9)	11 (6.3)	25 (7.3)	
employed	157 (30.3)	54 (30.7)	103 (30)	
Marital status				0.650
union/married	410 (79)	137 (77.8)	273 (79.6)	
single	109 (21)	39 (22.2)	70 (20.4)	
Baby´s father education				0.163
none	11 (2.1)	3 (1.7)	8 (2.3)	
primary	178 (34.3)	65 (36.9)	113 (32.9)	
secondary	126 (24.3)	39 (22.2)	87 (25.4)	
higher	38 (7.3)	19 (10.8)	19 (5.5)	
unknown	166 (32)	50 (28.4)	116 (33.8)	
Residence				1.000
urban	231 (45.3)	77 (45.3)	154 (45.3)	
rural	279 (54.7)	93 (54.7)	186 (54.7)	
Improved water				0.917
yes	377 (72.6)	127 (72.7)	250 (72.9)	
no	142 (27.4)	49 (27.8)	93 (27.1)	
Sanitation				0.516
yes	272 (52.4)	96 (54.5)	176 (51.3)	
open defecation	247 (47.6)	80 (45.5)	167 (48.7)	
Preconception factors				
Pregnancy planned				0.631
yes	126 (24.3)	41 (23.3)	85 (24.8)	
no	293 (56.5)	97 (55.1)	196 (57.1)	
missing	100 (19.3)	38 (21.6)	62 (18.1)	
Ever use of family planning methods				0.721
yes	106 (24.6)	33 (23.2)	73 (25.3)	
no	325 (75.4)	109 (76.8)	216 (74.7)	
Gravidity				0.389
1	126 (24.3)	37 (21)	89 (25.9)	
2–5	273 (52.6)	94 (53.4)	179 (52.2)	
≥5	120 (23.1)	45 (25.6)	75 (21.9)	

(*Continued*)

Table 2. (Continued)

Variables	TOTAL n = 519 (%)	ABO n = 176 n (%)	no-ABO n = 343 n (%)	*p*-value
Parity				
0	153 (29.5)	50 (28.4)	103 (30)	0.622
1–4	316 (60.9)	106 (60.2)	210 (61.2)	
≥5	50 (9.6)	20 (11.4)	30 (8.7)	
Previous abortion				0.158
yes	156 (30.1)	60 (34.1)	96 (28.0)	
no	363 (69.9)	116 (65.9)	247 (72.0)	
Previous stillbirth				0.068
yes	53 (10.2)	24 (13.6)	29 (8.5)	
no	466 (89.8)	152 (86.4)	314 (91.5)	
Poor birth spacing				0.815
yes	100 (19.3)	35 (19.9)	65 (19.0)	
no	419 (80.7)	141 (80.1)	278 (81)	
Previous cesarean section				0.592
yes	15 (2.9)	6 (3.4)	9 (2.6)	
no	504 (97.1)	170 (96.6)	334 (97.4)	
ANC				
GA at first ANC visit				0.835
≤12	272 (62.4)	91 (61.5)	181 (62.8)	
>12	164 (37.6)	57 (38.5)	107 (37.2)	
Number of ANC contacts				**<0.001**
1–4	75 (14.6)	31 (18.1)	44 (12.9)	
5–7	237 (46.2)	101 (59.1)	136 (39.8)	
≥ 8	201 (39.2)	39 (22.8)	162 (47.4)	
Obstetric ultrasound				0.777
yes	212 (40.8)	106 (60.2)	201 (58.6)	
no	208 (40.4)	70 (39.8)	142 (41.4)	
Twin pregnancy				**<0.001**
yes	34 (6.6)	24 (13.6)	10 (2.9)	
no	485 (93.4)	152 (86.4)	333 (97.1)	
Maternal anemia				0.978
yes	161 (31)	54 (30.7)	107 (31.2)	
no	240 (46.2)	81 (46)	159 (46.4)	
not done	118 (22.7)	41 (23.3)	77 (22.4)	
Bacteriuria				0.212
yes	155 (29.9)	44 (25.0)	111 (32.4)	
no	207 (39.9)	74 (42.0)	133 (38.8)	
not done	157 (30.3)	58 (33.0)	99 (28.9)	
Hyperglycemia				0.538
yes	16 (3.1)	7 (4.0)	9 (2.6)	
no	346 (66.7)	113 (64.2)	233 (67.9)	
not done	157 (30.3)	56 (31.8)	101 (29.4)	

(*Continued*)

Table 2. (Continued)

Variables	TOTAL n = 519 (%)	ABO n = 176 n (%)	no-ABO n = 343 n (%)	*p*-value
Malaria				1.000
yes	3 (0.6)	1 (0.6)	2 (0.6)	
no	385 (74.2)	131 (74.4)	254 (74.1)	
not done	131 (25.2)	44 (25)	87 (25.4)	
HIV				1.000
yes	3 (0.6)	1 (0.6)	2 (0.6)	
no	486 (99.4)	164 (99.4)	322 (99.4)	
Syphilis				0.340
yes	5 (1.1)	3 (1.9)	2 (0.6)	
no	463 (98.9)	154 (98.1)	309 (99.4)	
HsbAg				0.810
yes	16 (3.1)	4 (2.3)	12 (3.5)	
no	300 (57.8)	103 (58.5)	197 (57.4)	
not done	203 (39.1)	69 (39.2)	134 (39.1)	
Health facility-related factors				
Baby delivered at HAM				0.592
yes	504 (97.1)	170 (96.6)	334 (97.4)	
no	15 (2.9)	6 (3.4)	9 (2.6)	
Transferred from another unit				**0.009**
yes	21 (4.0)	13 (7.4)	8 (2.3)	
no	498 (96)	163 (92.6)	335 (97.7)	
Delivery assisted by				**0.011**
obstetrician	84 (16.2)	39 (22.8)	45 (13.5)	
midwife	421 (83.4)	132 (77.2)	289 (86.5)	
Intrapartum complications and mode of delivery				
Fetal malpresentation				0.607
yes	4 (0.8)	2 (1.1)	2 (0.6)	
no	515 (99.2)	174 (98.9)	341 (99.4)	
PROM				
yes	38 (7.3)	22 (12.5)	16 (4.7)	**0.002**
no	481 (92.7)	154 (87.5)	327 (95.3)	
Pre/Eclampsia				**0.029**
yes	37 (7.1)	19 (10.8)	18 (5.2)	
no	482 (92.9)	157 (89.2)	325 (94.8)	
Meconium-stained amniotic fluid				**0.027**
yes	90 (17.3)	40 (22.7)	50 (14.6)	
no	429 (82.7)	136 (77.3)	293 (85.4)	
Umbilical cord complication				0.355
yes	34 (6.6)	14 (8.0)	20 (5.8)	
no	485 (93.4)	162 (92)	323 (94.2)	
Obstructed labor				0.122
yes	52 (10)	23 (13.1)	29 (8.5)	
no	467 (90)	153 (86.9)	314 (91.5)	

(*Continued*)

Table 2. (Continued)

Variables	TOTAL n = 519 (%)	ABO n = 176 n (%)	no-ABO n = 343 n (%)	*p*-value
Postpartum hemorrhage				0.339
yes	1 (0.2)	1 (0.6)	0	
no	518 (99.8)	175 (99.4)	343 (100)	
Normal Vaginal delivery				**0.034**
yes	433 (83.4)	138 (78.4)	295 (86.0)	
no	86 (16.6)	38 (21.6)	48 (14.0)	
Cesarean section				**0.039**
yes	79 (15.2)	35 (19.9)	44 (12.8)	
no	440 (84.8)	141 (80.1)	299 (87.2)	
Instrumental vaginal delivery				0.694
yes	7 (1.3)	3 (1.7)	4 (1.2)	
no	512 (98.7)	173 (98.3)	339 (98.8)	
Newborns characteristics and complications				
Gestational Age				
<32	16 (3.1)	16 (9.1)	0	**<0.001**
32 a 37	76 (14.6)	76 (43.2)	0	
38–41	350 (67.4)	65 (36.9)	285 (83.1)	
≥41	77 (14.8)	19 (10.8)	58 (16.9)	
Sex				0.308
feminine	253 (48.7)	80 (45.5)	173 (50.4)	
masculine	266 (51.3)	96 (54.5)	170 (49.6)	
Birth weight				**<0.001**
<1500 g	17 (3.3)	17 (9.7)	0	
1500–2499 g	66 (12.7)	66 (37.5)	0	
2500–3999 g	415 (80)	72 (40.9)	343 (100)	
≥ 4000 g	21 (4.0)	21 (11.9)	0	
IUGR				**<0.001**
yes	21 (4.0)	18 (10.2)	3 (0.9)	
no	498 (96)	158 (89.8)	340 (99.1)	
Infectious risk				**<0.001**
yes	117 (22.5)	62 (35.2)	55 (16)	
no	402 (77.5)	114 (64.8)	288 (84)	
Neonatal resuscitation performed				**<0.001**
yes	28 (5.4)	26 (14.8)	2 (0.6)	
no	491 (94.6)	150 (85.2)	341 (99.4)	
Fetal distress at birth				**<0.001**
yes	103 (19.8)	72 (40.9)	31 (9.0)	
no	416 (80.2)	104 (59.1)	312 (91.0)	
Admission at NCU				**<0.001**
yes	70 (13.5)	64 (36.4)	6 (1.7)	
no	449 (86.5)	112 (63.6)	337 (98.3)	

(*Continued*)

Table 2. (Continued)

Variables	TOTAL n = 519 (%)	ABO n = 176 n (%)	no-ABO n = 343 n (%)	*p*-value
Received antibiotic				**<0.001**
yes	112 (21.6)	72 (40.9)	40 (11.7)	
no	407 (78.4)	104 (59.1)	303 (88.3)	

Bold text for p-value ≤0.05.

Abbreviations: GA–gestational age; ANC–antenatal care; PROM–prolonged rupture of membranes; IUGR–intrauterine growth restriction; NCU–neonatal care unit; HAM–Hospital Dr. Ayres de Menezes.

Note: Most pregnant women received tetanus toxoid vaccination, iron supplementation and blood pressure measurements, and these factors were not considered. All mothers stated no consanguinity with the baby's father and did not have smoking habits; therefore, these factors were also not included.

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STP. Multiple births (twins), meconium-stained amniotic fluid and PROM were all identified as significant associated factors for ABOs in the current study.

This study showed a rate of 17.7% PTB and 16% LBW, which are higher than the published estimates for STP of 12% PTB and 6.6% LBW [2,40,46]. In resource-constrained countries, one explanation for the difference found is the misclassification of late preterm babies (gestational age <37 weeks) in term babies [40,47]. Since gestational age in LMICs is mainly estimated from the date of onset of the last normal menstrual period, most times without ultrasound confirmation, mistakes are frequent [47].

Regarding LBW rates in the country, the source used is the UNICEF Multiple Indicator Cluster Surveys (MICS) [20,21]. MICS data rely upon the information provided by the mother about last birth in the previous two years and are associated with a higher risk of recall bias; therefore, these rate discrepancies between this study and official STP data can be linked to the above reasons. The lack of difference between the rate of PTB and LBW in this study is in line with the studies done in Nepal [48], Ethiopia [49] and Kenya [14] as biologically, a PTB has a higher risk of having LBW as they are less likely to get sufficient time for maturity, growth, and nutrient intake. Another important consideration is that most PTBs in this study were "late preterm" (76/92), often associated with a normal postnatal clinical course with no relevant complications, when compared to very preterm babies (16/92) [50].

The 1.5% congenital malformation and 4% macrosomia rates found in this study are similar to those described by other LMICs [4,8,36].

The neonatal sepsis rate published for LMICs ranges between 1.6% and 3.8% of all live births [50], with disparities among studies regarding the clinical algorithms used and the lack of gold-standard blood cultures for diagnosis [51,52]. This study 4% rate is in line with the overall LMIC rate but neonatal sepsis rates in STP are probably much higher since only babies diagnosed between the 24th and 36th hours of life were included; thus, all those with onset of sepsis after being discharged were missed out.

The 8.1% rate of birth asphyxia found in this study is lower when compared to other LMICs: a study in Ethiopia reports a pooled prevalence of 22.52%, 18% in other East African countries and 9.1% in some Central African countries [53,54]. The lower burden of asphyxia in STP may be due to differences in case definition, as in this study, birth asphyxia was only based on a fifth minute APGAR score less than 7, whereas other studies also used other criteria, such as umbilical cord pH < 7- or 20-min Apgar score less than 7 or multiorgan failure in the first 72 h or convulsion in the first 24 h of life [53]. APGAR scoring is also vulnerable to midwife evaluation and therefore susceptible to higher scoring for better health-related outcomes [26,27].

Table 3. Factors associated with adverse birth outcomes among newborns delivered at Hospital Dr. Ayres de Menezes in Sao Tome & Principe.

Variables	ABO n = 176 n (%)	no-ABO n = 343 n (%)	cOR (95% CI)	p-value	aOR (95% CI) p-value
Sociodemographic characteristics					
Maternal education					
none	7 (4)	12 (3.5)	1		
primary	111 (63.1)	187 (54.5)	1.02 (0.39–2.66)	0.972	
secondary	40 (22.7)	126 (36.7)	0.54 (0.20–1.48)	0.232	
higher	18 (10.2)	18 (5.2)	1.71 (0.55–5.35)	0.353	
ANC					
Number of ANC contacts					
1–4	31 (18.1)	44 (12.9)	1		
5–7	101 (59.1)	136 (39.8)	1.05 (0.62–1.78)	0.845	1.03 (0.59–1.78), p = 0.922
≥ 8	39 (22.8)	162 (47.4)	0.34 (0.19–0.61)	<0.001	0.33 (0.18–0.60), p <0.001
Twin pregnancy					
yes	24 (13.6)	10 (2.9)	5.26 (2.45–11.27)	<0.001	4.92 (2.25–10.74) p <0.001
no	152 (86.4)	333 (97.1)	1		
Intrapartum complications					
PROM					
yes	22 (12.5)	16 (4.7)	2.92 (1.49–5.72)	0.002	3.43 (1.69–6.95), p = 0.001
no	154 (87.5)	327 (95.3)	1		
Pre/Eclampsia					
yes	19 (10.8)	18 (5.2)	2.18 (1.12–4.28)	0.023	
no	157 (89.2)	325 (94.8)	1		
Meconium-stained amniotic fluid					
yes	40 (22.7)	50 (14.6)	1.72 (1.08–2.74)	0.021	1.59 (0.97–2.62), p = 0.068
no	136 (77.3)	293 (85.4)	1		
Health facility-related factors					
Transferred from another unit					
yes	13 (7.4)	8 (2.3)	3.34 (1.36–8.22)	0.009	
no	163 (92.6)	335 (97.7)	1		
Delivery assisted by					
obstetrician	39 (22.8)	45 (13.5)	1		
midwife	132 (77.2)	289 (86.5)	0.53 (0.33–0.85)	0.008	
Normal Vaginal delivery					
yes	138 (78.4)	295 (86)	1		
no	38 (21.6)	48 (14.0)	1.69 (1.06–2.71)	0.029	
Cesarean section					
yes	35 (19.9)	44 (12.8)	1.69 (1.04–2.74)	0.035	
no	141 (80.1)	299 (87.2)	1		
Newborns complications*					
IUGR					
yes	18 (10.2)	3 (0.9)	12.91 (3.75–44.47)	<0.001	
no	158 (89.8)	340 (99.1)	1		
Infectious risk					
yes	62 (35.2)	55 (16.0)	2.85 (1.87–4.35)	<0.001	
no	114 (64.8)	288 (84.0)	1		
Neonatal resuscitation					
yes	26 (14.8)	2 (0.6)	29.55 (6.93–126.11)	<0.001	

(*Continued*)

Table 3. (Continued)

Variables	ABO n = 176 n (%)	no-ABO n = 343 n (%)	cOR (95% CI)	p-value	aOR (95% CI) p-value
no	150 (85.2)	341 (99.4)	1		
Fetal distress at birth					
yes	72 (40.9)	31 (9.0)	6.97 (4.33–11.22)	<0.001	
no	104 (59.1)	312 (91.0)	1		
Admission at NCU					
yes	64 (36.4)	6 (1.7)	32.09 (13.53–76.13)	<0.001	
no	112 (63.6)	337 (98.3)	1		
Received antibiotic					
yes	72 (40.9)	40 (11.7)	5.24 (3.36–8.19)	<0.001	
no	104 (59.1)	303 (88.3)	1		

Abbreviations: ANC–antenatal care; PROM–prolonged rupture of membranes; IUGR–intrauterine growth restriction; NCU–neonatal care unit; cOR: Crude odds ratio; aOR–adjusted odds ratio; CI–confidence interval.

* Neonatal complications were related as a consequence of the case definition and therefore were not included in the multivariable model.

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The fivefold higher risk of multiple pregnancies having ABOs can be associated with the fact that monochorionic pregnancies have a vascular anastomosis within the placenta, affecting the perfusion of each twin and promoting adverse outcomes such as preterm labor, premature rupture of membranes, antepartum hemorrhage and fetal death [55]. Adverse outcomes in twin pregnancies were also reported in other studies [55–57]. As an example, some studies report that twin pregnancies have a thirteen-fold increase in rates of stillbirth in monochorionic pregnancies and a fivefold increase in dichorionic twins compared with singleton pregnancies [57]. Hence, the association between multiple pregnancies and ABO in this study reveals the importance of screening for multiple pregnancies as one key component of ANC to reduce the risk of ABO [56]. Other interventions to reduce ABOs related to twin pregnancies that can be recommended in STP are delivery at 37 weeks gestation in uncomplicated dichorionic twin pregnancies and delivery at 36 weeks in monochorionic pregnancies, as proposed by Cheong-See F et al. [57].

In this study, complete ANC with eight or more contacts was a protective factor, which should be expected, since ANC is the most important practice for mothers to obtain more information about nutrition and health, to perform screenings and to learn about danger signs regarding pregnancy and childbirth [16,22]. If a mother lacks ANC, minor obstetric conditions are not detected and managed early; therefore, serious complications and ABOs will likely develop [22,58]. Our finding is similar to the results from Ethiopia and other LMICs, in which ABOs, especially PTB and LBW, were higher among mothers with few ANC contacts [8,18,22,59]. This cutoff is linked to the fact that eight or more ANC contacts can reduce perinatal deaths by up to 8 per 1000 births when compared to only four ANC visits [60].

The rate of pregnancies with meconium-stained amniotic fluid in this study (17.3%) is similar to the international standard and from other studies in LMICs [10,61,62]. The occurrence of meconium-stained amniotic fluid during labor has long been considered a predictor of ABOs and an important sign of fetal distress associated with high rates of neonatal resuscitation, respiratory distress, lower Apgar score, birth asphyxia, neonatal care unit admissions and meconium aspiration syndrome [10,63]. Additionally, approximately 5–10% of neonates with meconium will experience meconium aspiration syndrome, which accounts for approximately 12% of neonatal mortality (as much as a 40% case fatality rate for the neonate and

approximately 2% of perinatal mortality) as well as for neonatal sepsis and pulmonary disease, representing an important risk factor not only for ABOs but also for death [10,63]. The odds of experiencing an ABO, in this study, were identified as being approximately twofold higher among meconium-stained fluid compared with a clear amniotic fluid at birth. Hence, early detection by using a latent follow-up chart and partograph and timely intervention is recommended to reduce this significant risk factor [10,63].

PROM was defined as rupture of the membrane lasting more than 18 hours before labor [37,43]. The overall rate in this study was 7.3%, which is in line with the estimated 5%-10% of all pregnancies in LMICs [64,65]. It was also identified as a significant risk factor for ABO, with a threefold higher risk compared to newborns without PROM. This is a well-known risk factor associated with early-onset neonatal sepsis and increased risk for perinatal mortality [64–67]. Thus, preventive measures should focus on the recognition of these high-risk newborns with early treatment with empirical antibiotics [64–67]. Such approaches would be a safe and cost-effective strategy, especially in STP where there are no laboratory culture techniques available.

In this study, no association was found between maternal infectious diseases (malaria, HIV, syphilis) and ABOs. This is mainly due to the fact that STP, in contrast to most SSA countries, is about to reach the elimination of HIV, syphilis, hepatitis B and malaria supporting the reduced number of mothers infected enrolled in this study [68,69]. Other viruses known to cause ABOs in SSA countries, such as Zika and dengue were not evaluated in this study since there is no evidence of Zika virus transmission in the country, and the first dengue fever outbreak in STP occurred two years after the completion of the field study [70]. Understanding the role and impact of environmental factors in ABOs is important, and contrary to expectations, no association was found between maternal sanitation behavior (open defecation) or type of access to water (no-improved) and ABOs, as reported in other LMICs studies [15,17,67].

Strengths and limitations

In this study, all clinical pregnancy-related information was abstracted from ANC cards and maternity registers to limit recall bias. Moreover, this study analyzed the main variables that are most frequently associated with ABOs in LMICs, including factors related to i) maternal health conditions, ii) infectious diseases, iii) environmental factors, iv) healthcare access, and v) obstetric interventions.

Regarding the limitations, maternal factors such as gestational weight gain, BMI, and height were not analyzed in this study, as these measurements are not performed during ANC contacts in the country, missing key mediators for ABOs [12]. Participants were asked about the weight gained during the pregnancy or their height, but mothers were not aware of either their height or weight gain. This lack of knowledge of basic one´s features and body conscience might also be due to the lack of scales and stadiometers in most healthcare facilities.

Notwithstanding these limitations, this study represents a significant first step in the description of ABOs and key modifiable associated factors in this resource-constrained setting.

Future research

The scope of this case-control study missed-out some recent areas of research, such as the impact of water contamination, traditional herbs, exposure to toxins on birth outcomes and long-term implications of ABOs on child development, growth, and health outcomes, which should be a matter of future research in this country [15–17]. This will promote further

understanding of the complex determinants of ABOs and provide new clues on how to improve birth outcomes and maternal and child health.

Conclusions

The high rates of ABOs could be reduced through the provision of high-quality intrapartum care, as twin pregnancy, meconium-stained amniotic fluid and PROM were identified as factors significantly associated with ABOs in this study. Having an ANC with 8 or more contacts was found to be protective, reinforcing the key strategy to reduce ABOs by providing a complete ANC service throughout the continuum of care.

Therefore, the modifiable associated factors found in this case-control study should be considered in cost-effective interventions. Reducing this ABO burden will not only impact neonatal mortality rates but will also promote child well-being, growth, and favorable health outcomes across their life course and provide substantial population-level human capital returns in this small and resource-constrained SSA country.

Supporting information

S1 File.
(XLSX)

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Factors associated with perinatal and neonatal mortality in Sao Tome & Principe: a prospective cohort study

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Abstract

Background

Neonatal mortality reduction is a global goal but its factors in high-burden nations vary and are poorly understood. This study was conducted to identify the factors affecting peri-neonatal mortality in Sao Tome & Principe (STP), the smallest Central Africa country.

Methods

Institution-based prospective cohort study conducted at Hospital Dr. Ayres Menezes. Maternal-neonate dyads enrolled were followed up after the 28th day of life (n=194) for identification of neonatal death-outcome (n=22) and alive-outcome groups (n=172). Data were collected from pregnancy cards, hospital records and face-to-face interviews. After the 28th day of birth, a phone call was made to evaluate the newborn's health status. A logistic regression model was used to identify the relevant factors associated with mortality. A p value <0.05 was considered statistically significant.

Results

The mean gestational age of the death-outcome and alive-outcome groups was 36 (SD=4.8) and 39 (SD=1.4) weeks, respectively. Death-outcome group (n=22) included sixteen stillbirths, four early and two late neonatal deaths. High-risk pregnancy score [cOR 2.91, 95% CI:1.18-7.22], meconium-stained fluid [cOR 4.38, 95% CI:1.74–10.98], prolonged rupture of membranes [cOR 4.84, 95% CI:1.47–15.93], transfer from another unit [cOR 6.08, 95% CI:1.95–18.90], and instrumental vaginal delivery [cOR 8.90, 95% CI:1.68–47.21], were factors significantly associated with mortality. The odds of experiencing death were higher for newborns with infectious risk, IUGR, resuscitation maneuvers, fetal distress at birth, birth asphyxia, and unit care admission. Female newborn [cOR 0.37, 95% CI:0.14-1.00] and birth weight of more than 2500 g [cOR 0.017, 95% CI:0.002-0.162] were found to be protective factors. In the multivariable model, meconium-stained fluid was significantly associated with death outcome.

Conclusion

Factors such as having a high-risk pregnancy score, meconium-stained amniotic fluid, prolonged rupture of membranes, being transferred from another unit, and an instrumental-assisted vaginal delivery increased 4– to 9–fold the risk of stillbirth and neonatal death. Of the factors associated with peri-neonatal mortality in this study, avoiding health-worker-related factors associated with delays in prompt intrapartum care is a key strategy to implement in Sao Tome & Principe.

Introduction

The first 28 days of life—the neonatal period—are the most vulnerable time for a child's survival, and a significant number die before birth never having the chance to take their first breath. Perinatal mortality includes stillbirths and early neonatal deaths (ENND), indicating the death of a live newborn before the age of seven completed days [1]. Late neonatal deaths (LNNDs) are those that occur after 7 days to 28 completed days of birth [2].

Globally, perinatal mortality accounts for three-fourths of deaths during the neonatal period [3,4]. More than half of the cases of stillbirths occur when pregnant women are in labor, and these deaths are directly related to the lack of skilled care at this critical time [5,6]. On the other hand, the largest contributors to neonatal mortality (ENND plus LNND) are complications of preterm birth, birth asphyxia, infection, and congenital malformations although they can differ depending on the country context [7].

Only in the last two decades, mainly after Lawn et al published article titled "4 million neonatal deaths: When? Where? Why?" [8], attention started to be given to the neonatal period in developing countries although stillbirths are still invisible and missing from the Sustainable Development Goals (SDG) agenda [5,9,10]. It urges to highlight that stillbirths and newborn deaths account for twice as many deaths as malaria and human immunodeficiency virus (HIV) infection combined but have received much less awareness and funding in these resource-constrained countries [8,9].

Understanding the causes of stillbirths (fetal deaths) is also complex, as there are many promoting and interacting factors [11]. In most low –to medium - income countries (LMICs), it is difficult to determine the exact reason for the stillbirth; therefore, the cause of death is often classified as "unexplained" [5]. Researchers report that different risk factors for fetal death, such as maternal factors (advanced maternal age, high pre-pregnancy body mass index, smoking, low socioeconomic status), obstetric history (grand multiparity, previous stillbirth), antepartum factors (fewer than four antenatal visits, fetal growth restriction, maternal anemia, maternal fever and infections, antepartum hemorrhage, hypertension), and intrapartum factors (preterm birth, extremes of neonatal birth weight, cesarean delivery, operative vaginal delivery, and assisted breech delivery), are all factors that have been reported in various studies as causes of stillbirths [6,11-15].

Sao Tome & Principe (STP) is an LMIC with low HIV/AIDS prevalence and a malaria pre-elimination phase [16,17]. There is an established antenatal care (ANC) service, with a 98% rate of women seen at least once by a skilled health provider during pregnancy and a 95.4% rate of deliveries occurring in health units [17]. In STP, perinatal and neonatal mortality is considered a public health problem in the country, given that neonatal deaths accounts for approximately 43% of all under5 deaths [18]. At the time this study was initiated, there was an annual rate of 22 stillbirths and 22 newborn deaths per 1000 livebirths [18].

We are aware that the concept of knowing what works in terms of reducing perinatal and neonatal mortality is complicated by a huge diversity of country contexts and of determinants of maternal and neonatal health [19-22]. However, according to Lawn and other authors, identifying and addressing avoidable causes of neonatal death is possible even in poorly functioning health systems, justifying our current study [8,9]. Answering - why, when, and where - newborns die in Sao Tome & Principe will enable the design of appropriate planning to prevent this major public health problem since, for appropriate prevention of fetal and newborn mortality, data pertaining to its determinants are important.

To the best of our knowledge, this is the first study to assess perinatal and neonatal mortality in STP, and it was undertaken within the context of a broader project on neonatal adverse birth outcomes (ABOs) in this LMIC [23-29].

Therefore, we conducted a prospective cohort study to identify the most important factors associated with mortality among newborns delivered at HAM.

Materials and methods

Study design and period

An institution-based prospective cohort study was conducted at Hospital Dr. Ayres de Menezes (HAM) for mother-neonate dyads followed up until the 28th day after delivery (neonatal period). Recruitment of participants (mother-newborn dyad) occurred from July 2016 to November 2018.

Setting

The archipelago of Sao Tome & Principe is one of the smallest sub-Saharan African (SSA) countries, with approximately 200.000 inhabitants and a total land surface of approximately 1,001 km2 on two islands (Sao Tome and a smaller island named Principe) [16,17]. The rural districts have ANC services and maternity units with basic obstetric services in Lembá, Lobata, Caué, Me-Zochi, and Principe Island, except for the district of Cantagalo. There is only one hospital in the country, Hospital Dr. Ayres de Menezes (HAM), with the only maternity in the country with Comprehensive Emergency Obstetric and Neonatal Care (EmONC) capable of providing blood transfusions and performing cesarean sections [30]. As a tertiary healthcare facility, HAM receives the most complicated cases from facilities in lower levels of care. There is no health insurance policy in the country or any private maternity units. In STP, there are three to four obstetricians, one anesthesiologist and one to two general doctors who provide care to the neonates [30]. There are no neonatologists in the country. The midwives in the labor ward are responsible for the initial resuscitation of normal deliveries, and doctors from the pediatric department are called to the labor ward to attend babies in distress.

The HAM maternity unit has a facility-based clinical care unit for ill newborn babies, but there is no neonatal or child intensive care unit in the country. The Neonatal Care Unit (NCU) receives high-risk babies delivered within the institution and referrals from other health facilities or from home with a total capacity to admit six babies. This unit, like others in SSA settings, is basic and able to manage simple neonatal complications such as hypothermia, feeding problems and sepsis suspicion. Although NCU was rebuilt in 2016, there is still a lack of continuous positive airway pressure therapy, surfactant therapy and enteric feeding for assisting sick babies.

Study population and follow-up

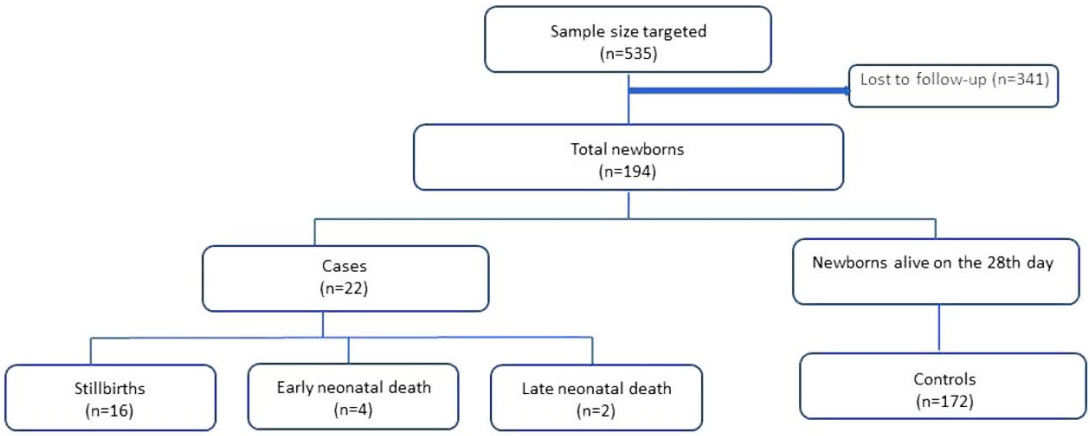
All mother-neonate dyads admitted to the HAM maternity unit for childbirth constituted the source population whereas the study populations were selected neonates delivered in the HAM maternity unit during the study period. During the study period, 4540 deliveries were recorded, corresponding to 450 cesarean deliveries and 3740 normal vaginal births.

The inclusion criteria for participants were as follows: 1) all neonates delivered at HAM with a gestational age of 28 weeks or more and 2) newborns who were born outside the hospital but were later admitted at HAM within the first 12 hours of life. A total of 535 newborns were initially enrolled.

The exclusion criteria included the following: 1) all neonates delivered at HAM with a gestational age of less than 28 weeks, 2) newborns whose mothers had no antenatal pregnancy card, 3) newborns whose mothers had cognitive impairment. The newborn was also excluded if his health status was unknown at his twenty-eight days of life.

Consenting participants in the sample were followed up (mother-newborn dyad) throughout their stays until hospital discharge. The survival status of neonates after discharge was ascertained by making a follow-up mobile phone call at the end of the neonatal period. Those who could not be reached by phone after four attempts in different weeks were taken as nonrespondents, and the mother-newborn dyad was excluded. A flowchart of participation in the study is shown in Fig 1.

Figure 1 Flowchart of participation in the study



Sampling method

This is a substudy undertaken to estimate adverse birth outcomes (ABOs) and related risk factors in the country.

The sample size initially calculated for the broader project, using Raosoft® (http://www.raosoft.com/samplesize.html), was based on the formula for sample size and margin of error from the software, reaching the minimum sample size of S = 355, with 355 (95%) and 579 (99%) interval confidence. The original study included 537 mother-neonate dyads enrolled based on the following assumptions: two-sided 95% confidence level, power of 80% to detect an odds ratio of at least two for ABO. Since the sample size was not calculated for present outcomes, to assess peri-neonatal mortality, a power analysis was performed, varying from 77% to 87% for outcomes such as gestational age (GA<37) for this study. In this study, 194 mother-neonate dyads were included. Participants were selected through random sampling. Each morning, from the pile of mothers´ medical folders, every second interval folder was selected and then carried on requesting contentment for enrollment. To guarantee a sample with few biases and effects by means of confounding variables, the

study was conducted in different months (two weeks every two other months), avoiding seasonal interference (rain season and malaria period). Women were interviewed only after the delivery, although the invitation and consent were obtained during her admission to the maternity unit before birth (live birth or stillbirth).

Selection of groups: death and alive neonatal outcome

A total of 194 mother-neonate dyads were included and were divided into two groups according to the newborn status (alive versus dead) at the end of the neonatal period. Newborns who died before the 28th day of life (death-outcome group with stillbirths included; n=22) were compared with newborns alive at the 28th day of life (alive-outcome group; n=172) concerning maternal, antepartum, and intrapartum characteristics.

Study Variables

The dependent variables for the study were death (stillbirth and neonatal - early and late -death) and live newborns.

The definition of stillbirth used was the WHO/ICD (for international comparison and reporting) as a baby born without any signs of life at or after 28 weeks of gestation or at least 1000 g in birth weight. [9,31]. Stillbirths were also described according to whether they were an intrapartum or antepartum stillbirth. Intrapartum stillbirth was defined as a dead-born fetus where intrauterine death occurred after the onset of labor and before birth (fresh stillbirth) [9]. Antepartum stillbirth is a dead born fetus where intrauterine death occurs before the onset of labor (macerated stillbirth) [9].

Neonatal mortality was defined as deaths in the first 28 days of life among live births. Death within the first 24 h (<24 h) or first day of life was recorded in units of completed minutes or hours of life [2]. Deaths occurring ≥24 h of life were recorded in days, from day 1 to 27 completed days [2]. The neonatal death definition used in this study was the one from the World Health Organization (WHO) as "deaths among live births during the first 28 completed days of life" [1], which were further subdivided into early neonatal deaths (ENND) as deaths between 0 and 7 completed days of birth and late neonatal deaths (LNND) as deaths after 7 days to 28 completed days of birth [2,32].

For neonates who died at home after discharge, probable causes of death were assigned by the principal investigator (pediatrician) using the International Statistical Classification of Diseases and Related Health Problems ICD-11 coding. For neonates who died in the HAM, the cause of death was assigned by physicians, who work in the hospital, and confirmed by the principal investigator.

The independent variables tested in this study included factors grouped into five categories: 1) newborns' maternal sociodemographic factors (age, educational status, occupation, marital status, partner's education, and residence); 2) preconception factors (previous contraceptive utilization), plus current obstetric condition (gravidity, parity, previous abortion and stillbirth, previous cesarean section and preceding birth interval); 3) ANC service (number of visits, gestational age at first ANC visit, obstetric ultrasound, number of fetuses in the ultrasound) plus antepartum factors as positive ANC

screenings (high-pregnancy risk score, maternal anemia as hemoglobin concentration <11 g/dl, bacteriuria, hyperglycemia, Rh incompatibility, intestinal parasitic infection (IPI), malaria, HIV, syphilis, hepatitis B virus and sickle cell); 4) health facility-related factors (being transferred from another unit, who assisted the delivery and partograph use) plus intrapartum factors as mode of delivery and complications (fetal malpresentation [33], umbilical cord complication [34], prolonged rupture of membranes (PROM) [35,36], meconium-stained amniotic fluid [37], postpartum hemorrhage as bleeding >500 mL, preeclampsia defined as hypertension ≥140/90 mmHg and proteinuria in dipsticks in women who were normotensive at ANC, and obstructed labor [38]); 5) newborns characteristics as (gestational age, sex, birth weight) and complications (intrauterine growth restriction (IUGR), congenital anomalies, infectious risk, neonatal resuscitation, fetal distress at birth, birth asphyxia and admission at NCU) [39-41].

Data collection

Data on antepartum, intrapartum, and postpartum characteristics of participants were gathered and collected from ANC pregnancy cards, obstetric maternal and newborn clinical records. For antepartum data, relevant details of the perinatal history and antenatal period were collected systematically from the ANC pregnancy card. Intrapartum data were collected from labor follow-up sheets, delivery summaries and maternal medical records. Postpartum data were abstracted from newborn birth charts and/or newborn medical records if admitted to the NCU.

Maternal sociodemographic characteristics were supplemented with a structured administered questionnaire through a face-to-face interview of the mothers 12-24 hours after delivery, similar to other studies from LMICs [42].

Data quality alive-outcome group

The questionnaires were administered in Portuguese, the country national language. The questionnaire was pretested at HAM one month before data collection in 23 mothers, and modification was made based on the pretest result, mainly adjusting terminology for more culturally friendly terms. Women´s consent to participate in the study was obtained at the time of admission at HAM, but the interview was held after a woman was stabilized and ready to be discharged. Continuous follow-up and supervision of data collection were made by the supervisors. The collected data were checked daily for completeness. The principal investigator (pediatrician) executed and was responsible for all main activities as follows: 1) obtaining consent and enrollment of the participants, 2) data collection from antenatal cards plus maternal clinical and newborns' records, 3) newborns' clinical observation (for diagnosis confirmation), 4) face-to-face interviews, 5) administering all phone interviews and 6) data collection entry into the database.

Data management

The anonymity and safety of the participants were ensured. Data were secured in a confidential and private location. Participants were referred to by identification numbers, and the informed consent

forms were kept separate from the questionnaires. Both could only be linked by a coding sheet available only to the principal investigator.

Data analysis

Data were entered into the QuickTapSurvey app (©2010-2021 Formstack), and the dataset was exported to Excel for cleaning and further analysis using the Statistical Package for the Social Sciences for Windows, version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). All data were checked for completeness and accuracy by the principal investigator and a qualified biostatistician.

Descriptive statistics, namely, frequencies and percentages were estimated. A univariable analysis was also performed. In this study, the neonatal death-outcome group was coded as 1, and the neonatal alive-outcome group was coded as 0. The proportion of missing data ranged from 0.8 to 10% across variables, and missing values higher than 10% were described in the analysis.

Univariable logistic regression analysis was used to estimate the unadjusted effect of each independent variable on the dependent variable. Variables that had a p value less than 0.25 were considered in the multivariable model. A p value < 0.05 was considered statistically significant in multivariable logistic regression analysis.

Ethics approval and consent to participate

The study complies with the Declaration of Helsinki and was approved and consented to by the Ministry of Health of Sao Tome & Principe and by the main board of Hospital Dr. Ayres de Menezes, since at the time the study protocol was submitted there was no ethics committee in STP. Only recently has the country's National Ethics Committee been appointed. Previously, study analysis and approval were performed by dedicated ethics oversight bodies, such as the Ministry of Health of Sao Tome & Principe and the main board of the Hospital Dr. Ayres de Menezes, and both approved this study.

Moreover, all methods in our study were performed in accordance with the relevant guidelines and regulations in practice.

Written informed consent was obtained from all participants after the purpose of the research was explained orally by the researcher. Approval by the participants´ parents or legal guardians was asked in the case of adolescents under 16 years of age or for illiterate women.

The participants or their legal representatives also consented to have the results of this research work to be published. Participation in the survey was voluntary, as participants could decline to participate at any time during the study.

Results

A total of 194 newborns were followed up during their first 28 days of life. In this study, the newborn's mean gestational age (GA) was 38.86 weeks with a standard deviation (SD) of 2.26 (minimum 28 - maximum 42 weeks). The death-outcome group (n=22) had a mean GA and birth weight of 36 (SD=4.83) and 2515 (SD=997) g, respectively, while their counterparts (172 in the alive-outcome group) had 39 (SD=1.41) weeks and 3209 (SD=507) g, respectively. The mean maternal age was 27.14 years, with a SD of 6.86 (minimum 15 - maximum 43) years old. The mean maternal age for the death-outcome group and alive-outcome group was 30.73 (SD=7.45) and 26.68 (SD=6.66) years, respectively.

The death-outcome group under-study included 16 stillbirths (72.7%), four (18%) ENND and two (9%) LNND. Stillbirths were 69% intrapartum stillbirths (fresh stillbirths), and 31% were antepartum stillbirths (macerated stillbirths). Stillbirth characteristics are further described in Additional file 1, and the early and late neonatal deaths (ENND and LNND) are described in Additional file 2.

The maternal characteristics as well as antepartum, intrapartum, and postpartum factors for the total of the participants and for the death-outcome group versus the alive-outcome group are described in Tables 1 and 2.

There were no maternal deaths in this study, with a total of 2 maternal near-misses occurring in the stillbirths' mothers´ death-outcome group numbers 5 and 11 that needed hysterectomy intervention due to atonic uterus with major obstetric hemorrhage.

Table 1 Univariable logistic regression analysis of peri-neonatal mortality among newborns admitted at HAM, Sao Tome & Principe (n= 194; death-outcome group :22 and alive-outcome group: 172)

Variables	Categories	Total n=194	Death-outcome group n=22 n (%)	Alive-outcome group n=172 n (%)	cOR	(95%) CI	p value
Sociodemographic characteristics							
Mother´s age	14-19	28 (14.4)	3 (13.6)	25 (14.5)	1		
	20-34	131 (67.5)	11 (50.0)	120 (69.8)	0.764	0.199-2.939	0.695
	≥35	35 (18)	8 (36.4)	27 (15.7)	2.469	0.588-10.36	0.217
Mother´s education	none+primary	106 (54.6)	19 (86.4)	87 (50.6)	1		
	secondary	88 (45.4)	3 (13.6)	88 (45.4)	0.162	0.046-0.566	**0.004**

Mother´s occupation	unemployed	139 (72.0)	16 (72.7)	123 (71.9)	1		
	employed	54 (28)	6 (27.3)	48 (28.1)	0.961	0.355-2.601	0.961
Marital status	union/married	124 (63.9)	14 (63.6)	110 (64)	0.986	0.392-2.482	0.977
	single	70 (36.1)	8 (36.4)	62 (36)	1		
Baby´s father education	none+ primary	63 (41.7)	9 (81.8)	54 (38.6)	1		
	secondary	88 (58.3)	2 (18.2)	86 (61.4)	0.14	0.029-0.67	**0.014**
Residence[1]	urban	92 (48.2)	9 (45)	83 (48.5)	0.867	0.342-2.200	0.765
	rural	99 (51.8)	11 (55)	88 (51.5)	1		
Preconceptional							
Contraception previous use	yes	38 (24.8)	3 (20)	35 (25.4)	0.736	0.196-2.760	0.649
	no	115 (75.2)	12 (80)	103 (74.6)	1		

Obstetric history							
Gravidity	1	42 (21.6)	4 (18.2)	38 (22.1)	1		
	2-5	100 (51.5)	8 (36.4)	92 (53.5)	0.826	0.235-2.907	0.766
	≥5	52 (26.8)	10 (45.5)	42 (24.4)	2.262	0.655-7.815	0.197
Parity	0	53 (27.3)	5 (22.7)	48 (27.9)	1		
	1-4	121 (62.4)	12 (54.5)	109 (63.4)	1.057	0.353-3.166	0.921
	≥5	20 (10.3)	5 (22.7)	15 (8.7)	3.200	0.814-12.574	0.096
Previous abortion	yes	59 (30.4)	6 (27.3)	53 (30.8)	0.842	0.312-2.272	0.734
	no	135 (69.6)	16 (72.7)	119 (69.2)	1		
Previous stillbirth	yes	17 (8.8)	4 (18.2)	13 (7.6)	2.718	0.801-9.225	0.109
	no	177 (91.2)	18 (81.8)	159 (92.4)	1		
Poor birth spacing2	yes	39 (20.1)	6 (27.3)	33 (19.2)	1.580	0.574-4.346	0.376
	no	155 (79.9)	16 (72.7)	139 (80.8)	1		
Antenatal care							
GA at first ANC visit	≤12	98 (60.5)	6 (27.3)	92 (53.5)	1		
	>12	58 (35.8)	9 (40.9)	55 (32)	2.509	0.847-7.430	0.097
Number of ANC visits	1-4	19 (10.1)	2 (10)	17 (10.1)	1		
	5-7	84 (44.4)	16 (80)	68 (40.2)	2.000	0.419-9.547	0.385
	≥ 8	86 (45.5)	2 (10)	84 (49.7)	0.202	0.027-1.538	0.123
Obstetric ultrasound	0	73 (38.4)	7 (35)	66 (38.8)	1		
	1	87 (45.8)	12 (60)	75 (44.1)	1.509	0.561-4.056	0.415
	2	30 (15.8)	1 (5)	29 (17.1)	0.349	0.041-2.976	0.336
Twin pregnancy	yes	14 (7.2)	0	14 (8.1)	-	-	-
	no	180 (92.8)	22 (100)	158 (91.9)	1		

Antenatal care screenings							
High-pregnancy risk[3]	yes	70 (36.1)	13 (59.1)	57 (33.1)	2.914	1.176-7.220	**0.021**
	no	124 (63.9)	9 (40.9)	115 (66.9)	1		
Maternal disease during pregnancy[4]	yes	123 (63.4)	11 (50)	112 (65.1)	0.622	0.244-1.587	0.321
	no	66 (34)	9 (40.9)	57 (33.1)	1		
	missing	5 (2.6)	2 (9.1)	3 (1.7)	4.222	0.618-28.867	0.142
Maternal anaemia[5]	yes	59 (30.4)	6 (27.3)	53 (30.8)	1.736	0.533-5.655	0.360
	no	98 (50.5)	6 (27.3)	92 (53.5)	1		
	not tested	37 (19.1)	10 (45.5)	27 (15.7)	5.679	1.892-17.048	0.002

Bacteriuria	yes	62 (32)	5 (22.7)	57 (33.1)	0.593	0.208-1.690	0.328
	no	132 (68)	17 (77.3)	115 (66.9)	1		
Hyperglycaemia[6]	yes	8 (4.1)	1 (4.5)	7 (4.1)	1.122	0.132-9.578	0.916
	no	186 (95.9)	21 (95.5)	165 (95.9)	1		
Rh incompatibility	yes	7 (3.6)	0	7 (4.1)	-	-	-
	no	187 (96.4)	22 (100)	165 (95.9)			
IPIs	yes	98 (50.5)	8 (36.4)	90 (52.3)	0.521	0.208-1.305	0.164
	no	96 (49.5)	14 (63.6)	82 (47.7)			
Malaria	yes	1 (0.5)	0	1 (0.6)	-	-	-
	no	193 (99.5)	22 (100)	171 (99.4)			
HIV	yes	2 (1.0)	1 (5.0)	1 (0.6)	1		
	no	192 (99)	19 (95)	163 (99.4)	0.123	0.007-2.037	0.143
HsAg positive	yes	6 (3.1)	2 (9.1)	4 (2.3)	1		
	no	113 (58.2)	10 (45.5)	103 (59.9)	0.194	0.032-1.195	0.077
Sickle cell positivity[7]	yes	13 (6.8)	1 (4.5)	12 (7.0)	0.631	0.078-5.102	0.666
	no	181 (93.2)	21 (95.5)	160 (93)	1		

Health facility-related factors							
Baby delivered at HAM	yes	188 (96.9)	21 (95.5)	167 (97.1)	1.590	0.177-14.275	0.679
	no	6 (3.1)	1 (4.5)	5 (2.9)	1		
Transferred from another unit*	yes	16 (8.2)	6 (27.3)	10 (5.8)	6.075	1.953-18.900	**0.002**
	no	178 (91.8)	16 (72.7)	162 (94.2)	1		
Delivery assisted by	obstetrician	36 (18.6)	5 (22.7)	31 (18)	1		
	midwife	153 (78.9)	16 (72.7)	137 (79.7)	0.724	0.247-2.126	0.557
	home labor	5 (2.6)	1 (4.5)	4 (2.3)	1.550	0.143-16.852	0.719
Partograph use	yes	76 (39.2)	9 (40.9)	67 (39)	1.085	0.440-2.678	0.860
	no	118 (60.8)	13 (59.1)	105 (61)	1		
Fetal malpresentation[8]	yes	2 (1)	0	2 (1.2)	-	-	-
	no	192 (99)	22 (100)	170 (98.8)			
PROM[9]	yes	15 (8.1)	5 (23.8)	10 (6.1)	4.844	1.473-15.930	**0.009**
	no	171 (91.9)	16 (76.2)	155 (93.9)	1		
Pre/Eclampsia[10]	yes	17 (8.8)	2 (9.1)	15 (8.7)	1.047	0.223-4.917	0.954
	no	177 (91.2)	20 (90.9)	157 (91.3)	1		
Obstructed labour[11]	yes	22 (11.3)	4 (18.2)	18 (10.5)	1.901	0.579-6.239	0.289
	no	172 (88.7)	18 (81.8)	154 (89.5)	1		
Postpartum haemorrhage[12]	yes	2 (1)	0	2 (1.2)	-	-	-
	no	192 (99)	22 (100)	170 (98.8)			
Normal Vaginal delivery	yes	155 (79.9)	15 (68.2)	140 (81.4)	0.490	0.185-1.300	0.152
	no	39 (20.1)	7 (31.8)	32 (18.6)			
Caesarean section	yes	33 (17)	4 (18.2)	29 (16.9)	1.096	0.345-3.477	0.877
	no	161 (83)	18 (81.8)	143 (83.1)			
Previous caesarean	yes	10 (5.2)	2 (9.1)	8 (4.7)	2.050	0.407-10.333	0.384
	no	184 (94.8)	20 (90.9)	164 (95.3)			
Instrumental vaginal delivery[13]	yes	6 (3.1)	3 (13.6)	3 (1.7)	8.895	1.676-47.208	**0.010**
	no	188 (96.9)	19 (86.4)	169 (98.3)			
	yes	43 (22.2)	11 (50)	32 (18.6)	4.375	1.744-10.975	**0.002**

Meconium-stained amniotic fluid	no	151 (77.8)	11 (50)	140 (81.4)			
Umbilical cord complication	yes	8 (4.1)	1 (4.5)	7 (4.1)	1.122	0.132-9.578	0.916
	no	186 (95.9)	21 (95.5)	165 (95.9)			

Newborn's characteristics							
Gestational Age[14]	28 - 31	3 (1.5)	3 (13.6)	0	1		
	32 - 36	8 (4.1)	4 (18.2)	4 (2.3)	-	-	-
	37 - 41	176 (90.7)	15 (68.2)	161 (93.6)	-	-	-
	≥42	7 (3.6)	0	7 (4.1)	-	-	-
Sex	feminine	92 (47.4)	6 (27.3)	86 (50)	0.375	0.140-1.004	**0.051**
	masculine	102 (52.6)	16 (72.7)	86 (50)			
Birth weight[15]	<1500 g	5 (2.6)	4 (18.2)	1 (0.6)	1		
	1500-2499 g	18 (9.3)	7 (31.8)	11 (6.4)	0.159	0.015-1.732	0.131
	2500g-3999 g	161 (83)	10 (45.5)	151 (87.8)	0.017	0.002-0.162	**<0.001**
	≥ 4000 g	10 (5.2)	1 (4.5)	9 (5.2)	0.028	0.001-0.564	**0.020**
IUGR[16]	yes	9 (4.6)	6 (27.3)	3 (1.7)	21.125	4.82-92.586	**<0.001**
	no	185 (95.4)	16 (72.7)	169 (98.3)	1		
Infectious risk[17]	yes	50 (25.8)	14 (63.6)	36 (20.9)	6.611	2.574-16.978	**<0.001**
	no	144 (74.2)	8 (36.4)	136 (79.1)			
Congenital malformation	yes	4 (2.1)	4 (18.2)	0	-	-	-
	no	190 (97.9)	18 (81.8)	172 (100)			

This is the Table 1 legend.

Abbreviations: ANC – antenatal care; CI – confidence interval; cOR: crude odds ratio; GA – gestational age; HAM: Hospital Dr. Ayres de Menezes; IPI – intestinal parasitic infection; IUGR – intrauterine growth restriction; PROM – prolonged rupture of membranes.

[1]Urban residence for women living in the capital city (Água Grande) and rural areas in all other districts (Mé-Zochi, Cantagalo, Lobata, Lembá, Caué and Principe Island).

[2]Poor birth spacing birth intervals of less than 2 years [43]

[3]High-pregnancy risk is registered in the ANC pregnancy card if the current pregnancy is defined as one or more of the following: 1) pregnant women age less than 15 years old or greater than 35, 2) grand multipara for women with six or more labors, 3) previous history of a stillbirth or early neonatal death, 6) previous caesarean section, and 7) previous hemorrhagic complication.

[4]Maternal disease was operationally defined as one or more of the following conditions during the current pregnancy: pre/eclampsia, gestational diabetes, malaria, bacteriuria, anemia, and intestinal parasitic infection.

[5]anaemia during pregnancy as a hemoglobin concentration <11 g/dl

[6]glycaemia >105 mg/dL,

[7]Through a sickle cell solubility test, which involves treating a thin blood film with sodium dithionate under hypoxic conditions and observing for sickling under a light microscope, that is the screening technique available in STP and performed to pregnant women with anemia or clinical suspicion. A positive result can suggest either sickle cell anemia or the sickle cell trait [44].

[8]Foetal malpresentation was determined if the presenting fetal part was noncephalic (e.g. breech, transverse, oblique) [33].

[9]Prolonged rupture of membrane (PROM) was defined as a rupture of membrane lasting longer than 18 hours before labor began [35,36].

[10]Preeclampsia (hypertension ≥140/90 mmHg and proteinuria in dipsticks in women who were normotensive at ANC).

[11]Obstructed labor was operationally defined as the sum of all cesarean sections due to mechanical problems or fetal distress and all instrumental delivery [38].

[12]Postpartum hemorrhage was defined as >500 mL bleeding.

[13] IVD in STP is only performed by vacuum.

[14]Gestational age was estimated from the date of onset of the last normal menstrual period or through ultrasound dating of pregnancy. Prematurity was defined as a delivery before 37 complete weeks of gestation from the date of onset of the last normal menstrual period and subcategorized as very preterm (28 to 31 weeks) and moderate to late preterm (32 to 37 weeks).

[15]Low birth weight was defined as a newborn weight less than 2500 grams (up to and including 2499 g) at birth regardless of gestational age. Low birth weight was further categorized into very low birth weight (VLBW, <1500 g) [45]. Low birth weight is a result of preterm birth, intrauterine growth restriction or both [45].

Large birth weight when ≥4000 g (macrosomia) irrespective of gestational age.

[16]There is still no consensual definition for intrauterine growth restriction (IUGR) or fetal growth restriction in Africa [46]. In this study, it was defined as the term LBW (i.e., birthweight <2500 g and gestational age ≥37 weeks of gestation) due to low in utero measurements through obstetric ultrasounds in the country [46].

[17]Infectious risk was operationally defined as the sum of all the following risk factors: 1) maternal fever (axillary temperature >37.9 C) at the time of delivery, 2) prolonged rupture of membrane (≥18 hours), and/or 3) foul-smelling amniotic fluid [47].

Factors associated with perinatal and neonatal mortality

Binary logistic regression analysis was performed to assess the association of peri-neonatal mortality with several characteristics (Table 1 and Table 2). Crude analysis showed that meconium-stained amniotic fluid, prolonged rupture of membranes, transfer from another unit, and instrumental vaginal delivery were significantly associated with peri-neonatal mortality.

Sociodemographic factors

A maternal secondary education level (cOR 0.162, 95% CI 0.46–0.566, p=0.004) and a baby´s father secondary education level (cOR 0.140, 95% CI 0.029–0.67, p=0.014) were found to be protective factors for peri-neonatal mortality.

Antepartum factors

The odds of peri-neonatal mortality were three times higher among mothers classified as having a high-pregnancy risk (cOR 2.91, 95% CI 1.18–7.22, p=0.021). Mothers without hemoglobin test during the ANC follow-up had a higher risk of having a peri-neonatal death (cOR 5.68, 95% CI 1.89–17.05, p=0.002) than those without anemia.

Health facility-related factors

The odds of peri-neonatal mortality were six times higher among mothers transferred from another unit compared to those directly admitted at HAM maternity (cOR 6.08, 95% CI 1.95–18.90, p=0.002).

Intrapartum factors

PROM as well as meconium-stained amniotic fluid were other intrapartum factors, with the odds of mortality being almost five times higher for newborns whose mothers had a PROM (cOR 4.84, 95% CI 1.47–15.93, p=0.009), and four times higher for those with a meconium-stained amniotic fluid (cOR 4.38, 95% CI 1.74–10.98, p=0.002).

For the mode of delivery, having an instrumental assisted delivery was associated with an eightfold higher risk of perinatal and neonatal mortality (cOR 8.90, 95% CI 1.68–47.21, p=0.010).

Newborns' factors

Newborns with intrauterine growth restriction had a twenty-one-fold higher risk of mortality (cOR 21.13, 95% CI 4.82-92.59, p<0.001), and newborns with an infectious risk had almost sevenfold higher odds of dying (cOR 6.61, 95% CI 2.57-16.98, p<0.001). Regarding newborn characteristics, female neonates (cOR 0.38, 95% CI 0.14-1.00, p=0.051) and birth weight greater than 2500 g and lower than 3999 g (cOR 0.017, 95% CI 0.002–0.162, p<0.001), and greater than 4000 g (cOR 0.028, 95% CI 0.001-0.564, p=0.020) were protective factors against peri-neonatal mortality.

Postpartum characteristics were only assessed for a total of six death-outcome group since sixteen stillbirths were not further included for analysis. Performance of neonatal resuscitation, fetal distress at birth (APGAR score at first-minute inferior to seven), birth asphyxia, and admission to the neonatal care unit were all related to an increased risk for neonatal mortality (Table 2).

Table 2 Univariable logistic regression analysis of neonatal mortality among newborns who were live births n= 178 [death-outcome group: 6 and alive-outcome group: 172]

Variables	Categories	Total n=178[ǂ]	Death-outcome group n=6[ǂ] n (%)	Alive-outcome group n=172 n (%)	cOR	(95%) CI	p value
Neonatal resuscitation	yes	7 (3.9)	2 (33.3)	5 (2.9)	16.700	2.457-113.495	**0.004**
	no	171 (96.1)	4 (66.7)	167 (97.1)	1		
Fetal distress at birth*	yes	26 (14.6)	5 (83.3)	21 (12.2)	35.952	4.004-322.859	**0.001**
	no	152 (85.4)	1 (16.7)	151 (87.8)	1		
Birth asphyxia**	yes	10 (5.6)	4 (66.7)	6 (3.5)	55.333	8.421-363.600	**<0.001**
	no	168 (94.4)	2 (33.3)	166 (96.5)	1		
Admission at NCU	yes	15 (8.4)	3 (50)	12 (7)	13.333	2.425-73.310	**0.003**
	no	163 (91.6)	3 (50)	160 (93)	1		

This is the Table 2 legend.

Abbreviations: CI – confidence interval; cOR: crude odds ratio; NCU – neonatal care unit.

[ǂ] stillbirths excluded

*Fetal distress was defined as a low Apgar score <7 at the first minute of life (score from 0 to <7) [24,48].

**Birth asphyxia was defined as a low Apgar score <7 at the fifth minute of life (score from 0 to <7) [24,48].

Multivariable model

Considering the small size of the outcome group (n=22), only one significant variable remained in the multivariable model. Newborns whose mothers had meconium-stained amniotic fluid were at a higher risk of peri-neonatal death.

Discussion

In this prospective cohort study, the main aim was to identify associated factors with perinatal and neonatal death. The most vulnerable period for death - partum, early or late neonatal period - and to identify where they die - in the maternity, at home or in the pediatric ward – was also possible as we were able to follow newborns up until their 28th day of life. In this study, we found that 90% died in HAM maternity before the 7th day of life, that is, during the perinatal period, with mainly being stillborn (73%). The magnitude of stillbirths observed in this study (3%) is in line with the studies conducted in Nigeria (4.8%) [49] and Tanzania (3.5%) [50] and lower compared with studies from Ethiopia (6.7%) [51]. Most stillbirths were intrapartum deaths, as also identified in LMICs similar to STP, and most could have been prevented [52,53].

In this study, intrapartum characteristics, such as pregnant women with meconium-stained amniotic fluid, prolonged rupture of membranes, and instrumental vaginal delivery, were the main factors significantly associated with perinatal and neonatal death. Health facility-related factors, as pregnant women transferred from another unit were also at a significant risk.

High-pregnancy risk score notification was the only antepartum factor significantly associated with peri-neonatal mortality. For newborns, experiencing fetal distress at birth, needing resuscitation maneuvers, having birth asphyxia and admission to the neonatal unit were identified as high-risk factors for death. Being a female newborn and having a birth weight greater than 2500 grams were found to be protective factors.

Odds of experiencing death were identified as four times higher among newborns from mothers with meconium-stained amniotic fluid. This finding is consistent with studies from Ethiopia [6,54] and Yemen [12] that also reported higher rates of fetal death due to intrauterine passage of meconium into amniotic fluid and a fivefold increase in perinatal mortality compared with low-risk patients with clear amniotic fluid [55]. Meconium-stained amniotic fluid is associated with fetal distress since the fetus, in response, inhales the meconium, which in turn leads to airway obstruction, surfactant dysfunction and pneumonitis, which leads to loss of the fetus [6].

PROM was also a significant factor associated with neonatal mortality in this study, showing fivefold higher odds for the death-outcome group. This association was also identified in other studies from low-resource constrained countries reporting one-third of stillbirths occurring during labor as a result of prolonged labor or obstructed labor not attended to promptly [39,40,42,56,57]. The reason for this might be because PROM is a risk factor for early-onset neonatal sepsis as well as a high risk of fetal distress, respiratory distress syndrome, intraventricular hemorrhage, and death [35,36,60]. In this study we found an overall prevalence of PROM of 8.1%, which is in accordance with the global incidence that ranges from approximately 5% to 10% of all deliveries in the world [58,59].

Lack of emergency obstetric care (EmOC) is well-known to increase the risk of neonatal mortality, as laboring mothers with complications cannot immediately receive appropriate health services, such as access to a cesarean section [40]. In this study, mothers who needed to be transferred from another health unit for delivery at HAM had a sixfold higher risk of having a neonatal death outcome than mothers directly admitted at HAM. Half the mothers who were transferred from the death-outcome

group had to do a 60 -kilometer journey that took approximately two to three hours until reaching HAM maternity in the capital city. Distance from a health facility with EmOC and the considerable travel times are well-known barriers and influential factors of birth adverse outcomes also found in other studies in sub-Saharan Africa [60,61].

In this study, the overall rate of 3.1% of instrumental assisted vaginal birth deliveries was found to be lower compared to 17% of births by cesarean section and 79.9% of normal vaginal deliveries. Instrumental-assisted deliveries are an effective intervention for deliveries complicated by prolonged labor or fetal distress but are also related to adverse outcomes since fetal distress or cephalopelvic disproportion are more frequently the motive to use this technique. Therefore, the ninefold higher risk of death outcome found in this study, similar to other researchers reporting [13,62,63], relates to late appropriate intrapartum care intervention with subsequently higher rates of fetal distress and risk of an intrapartum stillbirth.

Antenatal care health services in STP follow a high-risk stratification for each pregnancy and, in this study, this notification of a high-risk pregnancy in the pregnant women antenatal pregnancy card was significantly associated with a threefold higher risk for fetal and neonatal death than alive-outcome group. High-pregnancy risk was operationally defined as one or more of the following according to STP national practice, namely, age as inferior to 15 years old or superior to 35, grand multipara, previous history of a stillbirth or early neonatal death, previous cesarean section, and previous hemorrhagic complication. This is consistent with other studies that reported higher rates of perinatal and neonatal mortality with extreme maternal ages and previous adverse obstetric history (grand multipara, previous stillbirth, or early neonatal death) [1,12]. However, in this study, we could not find a statistically significant difference between groups when each of these variables were independently analyzed.

Regarding the newborns' characteristics, the overall sex ratio at birth was 52.6% for males and 47.4% for females. The death rate was higher in male neonates (72%) than in the female death-outcome group (27.3%), with female sex being a protective factor. Sex variations are frequently reported, with a highly consistent pattern of excess male mortality across different populations and income groups [64]. Male infants are more vulnerable to fetal and early neonatal death, with most studies reporting no gender difference in mortality after 7 days of age [64]. This sex difference may be explained by a sex-specific difference in the growth and function of male and female placentae, making boys more vulnerable to different adverse outcomes [64-66].

Birth weights of more than 2500 g were protective factors for death outcome in this study. This finding is comparable with different research on other African countries that associates a birth weight of less than 2500 g (LBW) with higher rates of stillbirth and neonatal death [1]. Additionally, the odds of experiencing death were 21 times higher for babies with IUGR or fetal growth restriction defined, in this study, as a term LBW (birthweight <2500 g and gestational age ≥ 37 weeks) [46]. Low birth weight is a worldwide recognized important multifaceted public health problem since LBW infants are 20 times more likely to develop complications and die than normal weight infants [6,67].

We found that the odds of death were six times higher for newborns with maternal infectious risk. This finding is in agreement with previous studies conducted in SSA, as neonatal infectious risk is linked to amniotic fluid contamination that can cause intrapartum fetal infection or early postpartum neonatal infection with sepsis complicated with septic shock and multiple organ dysfunction, in which both are the most common causes of death in the perinatal period [39,47]. Infection is an important cause of stillbirth and neonatal death in LMICs, although there is a lack of overall information regarding the

organisms involved, the types of transmission, and the mechanisms of death in these constrained countries [68]. In Sao Tome & Principe, malaria and syphilis are no longer an infection-burden and cause of stillbirth or neonatal death; therefore, other bacterial and viral maternal infections should be linked to stillbirth and ENND [68]. In STP, there are no means to establish a neonatal infection through blood cultures; that is, neonatal infection is based only on clinical signs with no bacteriological documentation. Additionally, nothing is known about the rate of vertical transmission of Streptococcus Group B (GBS) from colonized mothers at birth in the country. Therefore, there is a current gap in the knowledge, capability of making diagnosis and prevention and treatment of neonatal infections in STP. For instance, a study from Ethiopia [68] detected that the rate of vertical transmission of GBS from colonized mothers at birth was as high as 45.02% due to term PROM, PROM ≥18 hours before delivery and mothers having fever during labor. Detecting the risk for vertical transmission of GBS and implementing prevention methods such as adequate intrapartum administration of antibiotics are recognized as easy and affordable practices for reducing mortality due to infectious causes and should be implemented in the country along with culture techniques [47].

All four congenital major malformations detected in this study resulted in perinatal mortality, although due to the low number of newborns enrolled it was not possible to establish a statistically significant difference. Congenital malformations are known to be associated with poor outcomes for newborns, and 10–20% of stillbirths are attributed to intrinsic fetal anomalies [57]. Studies from Zimbabwe [69], Ethiopia [1] and Yemen [12] found that congenital anomalies among stillbirths were associated with a 5-fold [69], 34-fold [1] and 40- fold [12] higher risk than those among live births. Another important consideration regarding congenital anomalies is the type of malformation, since some, such as neural tube defects, are preventable and can be reduced by 30 to 50% by folic acid supplementation in pregnant women and have been estimated to cause 29% of deaths related to congenital anomalies in LMICs [4]. In this study, three out of the four major anomalies were neural tube defects, highlighting the need to enhance proper supplementation to preconceptional women in the country.

In this study, we were not able to find a higher risk associated with newborn gestational age. The high rate of stillbirths found in our study as well as the low number of preterm babies enrolled (5.6%) explain the lack of association. Stillbirths are among the most common pregnancy-related adverse outcomes worldwide, but they differ between low- and high-income countries. In high-income countries, most stillbirths occur early in the preterm period, whereas in low-resource constrained countries, most occur in term or in late preterm births, as found in our study [70]. Additionally, the neonatal mortality is higher in babies born between 37 and 38 weeks of gestation than in those born between 39 and weeks [4].

From stillbirths in this study, 69% occurred during the intrapartum period, in accordance with other studies from LMICs [5]. These intrapartum stillbirths mean that intrauterine death occurred after the onset of labor and before birth (fresh stillbirth). We can also guess that some of them could be early neonatal deaths, as there are known barriers and difficulties in these contexts to establish whether a fetus or motionless newborn is living or dead after its delivery. For instance, information on some Apgar scores in these death-outcome group was not recorded, perhaps because of lack of time, especially when the neonates had to be rushed to receive resuscitation maneuvers. Studies from SSA highlight that it is very frequent that some depressed but living fetuses with a possible heartbeat do not receive resuscitation maneuvers and are prompt classified as stillbirths [1,70]. This is supported by a systematic review of sixteen hospitals and community-based perinatal mortality studies [71,72].

In this study, newborns who needed resuscitation maneuvers were at a 16-fold higher risk of dying. Additionally, the odds of neonatal death from fetal distress at birth and birth asphyxia were 36 and 55 times higher, respectively. These results are in line with studies conducted in Cameroon [73] and Ethiopia [40] as well as published literature that suggests that lower APGAR scores are associated with severe multiorgan damage resulting in brain damage, lung dysfunction, cardiomyopathy, renal failure, hepatic failure, necrotizing enterocolitis and consequently death [74]. Previous studies conducted by the authors, that compared outcomes between adolescent pregnant girls and older counterparts identified that adverse outcomes imputable to adolescent births were fetal distress and performance of neonatal resuscitation maneuvers, highlighting the risks surrounding this period among deliveries at HAM maternity unit [23,24].

Perinatal asphyxia can be caused by factors grouped according to whether they are before birth (antepartum risk actors), during birth (intrapartum risk factors), or after birth (postpartum or fetal risk factors) [48,74]. Nonetheless, the single most important predictor is, undoubtedly, the quality of intrapartum care during labor and delivery.

The most important aspect of this study for public health is that it identifies potential characteristics that predispose newborns to life-threatening conditions, which is critical to address the underlying causes and provide prompt interventions by various stakeholders in the healthcare system [75].

This study allows us to perceive how to answer our question "when, where and why do newborns die in STP?" as "when": mostly during labor, "where": in uterus and "why": mainly due to fetal distress and intrapartum-related deaths probably due to low quality and constraints of care during labor and delivery. Ending preventable stillbirths and neonatal deaths does not necessarily require new or innovative interventions. Most modifiable risk factors identified in this study can be addressed and prevented with timely, quality care during childbirth, including ongoing intrapartum monitoring and opportune intervention in case of complications [76]. Some interventions, such as computerized cardiotocography to monitor a baby's well-being in the womb by measuring contractions, are estimated to reduce the rate of infant deaths around the time of birth by 80% when compared with traditional cardiotocography [77].

In summary, the findings of this study will be useful to health policymakers and program developers in implementing appropriate interventions to achieve the newborn health post-2015 Sustainable Development Goals of no more than 12 neonatal deaths per 1000 live births in Sao Tome & Principe by 2030 [78].

Strengths and Limitations

In this study, the researcher retrieved maternal and neonatal data directly from ANC cards and maternity registers to limit recall bias. The selection of the death-outcome group and alive-outcome group was based on the records of maternal and neonatal registers; therefore, it is less likely that this study has misclassification biases both in the exposure and death-outcome group –alive-outcome group categories [79].

Regarding the limitations, this is a relatively small study aiming to identify factors associated with peri-neonatal mortality in Sao Tome & Principe with a cohort of 194 newborns that were followed up until 28th days of age, 22 died and 172 survived. Thus, this study results cannot be generalized.

Another limitation is that some of the variables mentioned in the univariable model had wide confidence intervals and high odds ratios due to the low number of death-outcome group enrolled in this study. This was a barrier to conducting a multivariable model, a limitation also reported in other studies [41]. Due to the small number of neonatal death-outcome group enrolled and these wide confidence intervals, the multivariable logistic regression model could only identify one independent determinant of mortality outcome.

Nonetheless, the current study can assist Sao Tome & Principe policy makers and stakeholders in designing new policies for the country to improve maternal and neonatal health outcomes.

Conclusions

Complications such as a high-risk pregnancy score, meconium-stained amniotic fluid, prolonged rupture of membranes, being transferred from another unit, and an instrumental-assisted vaginal delivery increased the risk of stillbirth and neonatal death between 4– and 9–fold, and 90% of all these deaths occurred in the perinatal period.

Newborns with an infectious risk, intrauterine growth restriction, fetal distress at birth, who needed resuscitation maneuvers, birth asphyxia, and those admitted to the neonatal unit had a 3- to 55-fold higher risk for dying than the alive-outcome group. Female newborn and birth weight of more than 2500 g were found to be protective factors.

Implementing an efficient referral system that directs high-risk pregnancies to the EmOC facility, equipment (continuous fetal heart monitoring capability in all district maternity wards) and personnel technical skills will improve peri-neonatal outcomes and survival in Sao Tome & Principe.

Additional Requirements

1 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

2 Author Contributions

AV, MCM and FP carried out the conception and design of the study. AV was responsible for field activities, data collection, and wrote the manuscript. MCM critically evaluated and made progressive suggestions throughout the study and revised the manuscript. MA and ALP performed statistical analysis and reviewed the manuscript. SS and NB were involved in the study design at the country level. All the authors read and approved the final draft of the manuscript.

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Supplementary Material

Supplementary Material

Additional file 1: stillbirths' characterization

Additional file 2: early and late neonatal deaths characterization

Data Availability Statement

The datasets used and/or analyzed during the current study are all available within the manuscript itself.

Additional file 1 Death-outcome group: characteristics of the stillbirths (n=16)

Stillbirth number	Intrapartum stillbirths	Gestational age range[ł]	sex	Birth weight	Major malformation	Pregnant Transferred	Reason for transferred	PROM	Meconium	Eclampsia	Atonic uterus	Birth attendant	Dystocia
1	no	4	male	3100	yes*	yes[1]	no fetus heartbeat	-	yes	-	-	midwife	no
2	no	1	male	1200	-	yes[1]	no fetus heartbeat	-	-	-	-	midwife	no
3	no	4	male	2000	-	yes[2]	eclampsia	-	yes	yes	-	midwife	no
4	yes	4	male	1900	-	-	-	-	yes	-	-	midwife	no
5	yes	4	male	2900	-	-		-	-	-	yes	obstetrician	yes
6	no	2	female	980	-	yes[3]	no fetus heartbeat	-	-	-	-	midwife	no
7	yes	3	female	1750	-	-	-	-	-	-	yes	obstetrician	yes
8	yes	4	male	3300	-	-	-	-	yes	-	-	midwife	no
9	yes	3	male	1600	-	-	-	yes	-	-	-	midwife	no
10	yes	4	male	3000	-	-	-	yes	-	-	-	obstetrician	yes
11	yes	4	female	1900	-	-	-	-	-	yes	-	midwife	no
12	no	4	male	3100	yes*	yes[1]	no fetus heartbeat	yes	yes	-	-	midwife	no
13	yes	4	male	2000	-	-	-	-	yes	-		midwife	no
14	yes	4	male	3500	-	-	-	-	-	-	--	midwife	yes
15	yes	1	male	1200	-	-	-	yes	yes	-	-	midwife	yes
16	yes	4	female	3990	-	-	-	-	yes	-	-	midwife	N0

This is the Table 1 legend.

*Malformation in two stillbirths: Multiple malformations in the rib cage, spina bifida, clubfoot and hydrocephalus

[1] Caue district, [2] Cantagalo, [3] Lobata

[ł]sub-categories of preterm birth, based on gestational age: 1=extremely preterm (less than 28 weeks); 2=very preterm (28 to 31 weeks); 3=moderate to late preterm (32 to 36 weeks); 4=term newborns (37 to 41) and 5= posterm newborn (>42)

Additional file 2 Death-outcome group: characteristics of the six live births with a neonatal death (n=6)

Neonatal death	Time of death (range)	Main cause of death	Sex	Birth weight	Prematurity	Major malformation	Birth asphyxia	NCU admission	PROM	Meconium	Eclampsia	Birth attendant	Dystocia
[†]ENND 1	< 24h	Prematurity-related death	male	1230	yes	no	no	yes	yes	yes	no	home delivery	no
ENND 2	< 24 h	Major malformation + Birth asphyxia	male	3000	no	yes*	yes	yes	no	no	no	obstetrician	yes
ENND 3	Day 1-7	Sepsis + Birth asphyxia	male	2200	yes	no	yes	yes	no	yes	yes	midwife	no
ENND 4	Day 1-7	Major malformation + Birth asphyxia	female	3450	no	yes*	yes	yes	no	yes	no	midwife	no
LNND 5	Day 8-10	Sepsis + Birth asphyxia + Brachial plexus lesion	male	4250	no	no	yes	yes	no	yes	no	midwife	no
LNND 6	Day 10-15	Probably late sepsis	female	3800	no	no	no	no	no	no	no	obstetrician	yes

This is the Table 2 legend.

Abbreviations: ANC – antenatal care; NCU – Neonate Care Unit; PROM – prolonged rupture of membranes; yo – years old; ENND – early neonatal death.

*Major malformations identified ENND 2: hydrocephaly and ENND 4: thoracic malformation

[†]Maternal characteristics: ENND 1 (mother age range 35-40 years old, G7 P6, 1 ANC visit); ENND 2 (mother age range 15-19 years old, G0 P0, 6 ANC visits); ENND 3 (mother age range 20-24 years old, G1 P0, 4 ANC visits); ENND 4 (mother age range 35-40 years old, G6 P5, 4 ANC visits); LNND 1 (mother age range 35-40 years old, G5 P3, 8 ANC visits); LNND 2 (mother age range 35-40 years old, G2 P1, 6 ANC visits).

Chapter 4 |

1 | Discussion

Perinatal mortality is a major public health problem in Sao Tome & Principe, as reinforced by this research.

A total of twenty-two (4%) perinatal and neonatal deaths occurred in the 535 mother-birth-dyads enrolled in this study. Deaths occurred mainly (95.4%) at Hospital Dr. Ayres de Menezes (HAM), from which 16 (72.7%) were stillbirths delivered in the labour room plus four (18.2%) early neonatal deaths at the Neonatal Care Unit (NCU). One (4.5%) late neonatal death also occurred in the NCU. In the prospective cohort study, the follow-up mobile phone call allowed to know the health status of 194 newborns after the 28th day of life, with one (4.5%) late neonatal death identified.

These results indicate a probability of a stillbirth in 30 per 1000 liverbirths, and a probability of neonatal death rate range of 11 (lower limit) and 31 (upper limit) per 1000 livebirths (lower limit for the 194 cohort and upper estimation for the 535 dyads enrolled), values almost up to two times higher than the rates estimated for the country (1, 2). To note, that the most up-to-date stillbirth rate range published for the country is 5.5 to 14.67 stillbirths per 1000 livebirths and the neonatal mortality rate range is 4.34 to 14.53 neonatal deaths per 1000 livebirths (1).

Therefore, in this study, the perinatal period was identified as the most vulnerable stage, with 91% of all deaths, mainly due to the high rate of stillbirths. This is a reality shared with other similar settings (6). The 3% rate of stillbirths observed in this study is in line with other low- and low- middle-income countries (LLMICs), such as Tanzania with 3.5% (7), and Nigeria with 4.8% (8), but lower when compared with 6.7% from Ethiopia (9). Moreover, it was observed that most were intrapartum stillbirths (69%), as also described in similar settings, highlighting the need to scale-up intrapartum interventions at the HAM maternity unit, since most intrapartum stillbirths are preventable (10-12).

Moreover, deaths identified in this research do not include all neonatal deaths due to the number of losses to follow-up in the prospective cohort study, underestimating the real number of deaths. Furthermore, for this study period, there is also no official data regarding how many neonatal deaths occurred in the NCU, in the paediatric ward or in the emergency room of HAM, nor at the community level, but additional studies conducted during this thesis research period provide some insights.

First, a retrospective study was conducted at the paediatric ward of HAM describing the causes and outcomes of admissions for a 10-month period (Appendix 13). From 1963 admissions of children under 24-months-old, a total of 52 (5%) were newborns, who were admitted due to probable neonatal sepsis 27% (14), respiratory distress 15% (8) and whooping cough suspicion 10% (5) (3). From a total of eleven children (0.6%) under two-years-old deaths, only one (9%) neonatal death, due to probable sepsis was identified (3).

Second, in another retrospective study, from a total of 948 newborns admitted to the NCU at HAM, 16.2% were premature (1.7% extreme, 3.8% very, 10.7% late preterm) (Appendix 4). The most common reasons for admission were infectious risk with meconium-stained amniotic fluid (25.2%), probable early-onset sepsis (17.1%), prematurity-related complications (9.8%), asphyxia (6.1%), congenital anomalies (3.5%), and HIV-MTCT treatment (3.1%). The average length of stay was 5.5 days (SD 7.8). The overall mortality rate was only 6% (57), with 20% (200) missing discharge information. Since discharge information was missing for 20% of cases, it is presumed that the rate of neonatal deaths in the NCU at HAM is higher.

With all the above considerations in mind, the perinatal and neonatal mortality rates are perceived as even higher than the ones recognized through this research. Nonetheless, this study has provided answers to newborns´ *"when, where and why*" deaths.

Mostly are stillbirths; consequently, *when*? during labour, *where*? in the maternity unit, *why*? mainly due to intrapartum complications and healthcare service-related factors.

Considering the remaining neonatal causes of deaths, most were related to having additive (more than one) adverse birth outcomes (ABOs), namely, two newborns died due to major malformations and birth asphyxia, two due to probable early-onset sepsis and birth asphyxia, one due to prematurity-related complications (birth weight 1230 g), and one due to probable late onset sepsis.

Regarding neonatal factors associated with perinatal and neonatal deaths, having an intrapartum infectious risk, intrauterine growth restriction, foetal distress at birth, needing resuscitation manoeuvres, birth asphyxia, and admission to the neonatal unit were significantly associated with a 3- to 55-fold higher risk of neonatal death. These associated factors were also identified in LLMICs similar to STP, and most could have been prevented (11-13).

Being a female newborn and having a birth weight of more than 2500 g were found to be protective factors. This is in accordance with the literature since boys are recognized to have a higher biologic risk of neonatal death (14) and having a birth weight greater than 2500 g is considered to be a protective factor (5).

Concerning neonatal morbidity, the following ABOs were studied: prematurity (PTB), low birth weight (LBW), congenital anomaly, birth asphyxia, macrosomia, and neonatal sepsis suspicion. In the case-control study conducted, a total of 519 newborns (176 with ABO and 343 with no-ABO) were enrolled (stillbirths were excluded), and 34% had a child-related ABO, with 17.7% PTB, 16% LBW, 8.1% birth asphyxia, 1.5% congenital malformation, 4% macrosomia and 4% probable neonatal sepsis.

The study rates of PTB and LBW are higher than the published estimations for Sao Tome & Principe of 12% PTB and 6.6% LBW (15, 16). In resource-constrained countries, one explanation for the difference found is the misclassification of late preterm babies in term babies (17, 18). Since gestational age in this setting is mainly estimated from the date of onset of the last normal menstrual period, most times without ultrasound confirmation, mistakes are frequent. Moreover, midwives may tend to record a higher gestational week in the newborn's record upon a baby's healthy vitality at birth (17).

In this study, 82.6% (76 out of 92 PTB) were moderate to late preterm (32 to 37 gestational week), with a normal postnatal clinical course with no relevant complications for these PTB when compared to very preterm babies (19).

During this research and the period of follow-up of the premature babies enrolled who were admitted to the NCU, the main interventions for PTB and LBW available in this unit were assessed. Regarding preterm care, 16 out of 92 PTB (17.4%) were extremely preterm babies (gestational age <32 weeks) with special needs. However, there were no manoeuvres or techniques implemented, such as hypothermia prevention or kangaroo mother care implemented at this NCU. Moreover, skin-to-skin contact for PTB and LBW babies is not promoted immediately after birth, and a delay in cord clamping in preterm newborns for the prevention of anaemia is not implemented. Additionally, other healthcare service-related deficits were perceived, since there are no neonatal intensive care units in the country or any facilities with mechanical ventilation, continuous positive airway pressure (CPAP), or surfactant therapy. STP is a small country with the double burden of being an island far away from everywhere else and without any proper support available for newborns. There is no possibility of transferring sick and small babies to other neonatal units in nearby countries. Thus, STP does not meet the UNICEF policy of the right of every newborn everywhere on having access to a high-quality universal newborn healthcare. Moreover, STP also misses Every Newborn Action Plan call for 80% of districts of sub-Saharan Africa (SSA) to have at least one hospital that provides Level 2 inpatient newborn care by 2025, including respiratory support with CPAP (20, 21). Underlining the current major gaps in neonatal care in Sao Tome & Principe. As widely known, adequate intervention for neonatal complications, help to reduce neonatal mortality (section 3. Part II, Chapter 1), and strategies to upscale neonatal care at HAM are urgently needed (5, 21-23).

Regarding other ABOs, the 1.5% congenital malformation, 4% macrosomia and 4% neonatal probable sepsis rates are consistent with the findings of similar studies performed in LLMICs (19).

In settings with no blood cultures available, neonatal septicaemia ranges from 1.6% to 3.8% of all livebirths, in accordance with this study (24, 25).

The 8.1% prevalence of birth asphyxia is lower than that in other settings, such as 22.52% in Ethiopia, 18% in East African countries and 9.1% in some Central African countries (26). The lower birth asphyxia rate in STP can be linked to previous interventions implemented, such as the training of all countries´ midwives in neonatal resuscitation skills (Appendix 7) (27).

One important consideration regarding congenital anomalies is the type of malformation, since some, such as neural tube defects, estimated to cause 29% of deaths in LLMICs, are preventable and can be reduced by 30 to 50% by folic acid supplementation in pregnant women (28, 29). In this research, three out of the four major anomalies found were neural tube defects, that is, amenable to prevention, highlighting the need to enhance proper preconception supplementation to women in STP.

Risk factors for ABOs and mortality can overlap but are not the same across different cultures, socioeconomic statuses and healthcare service quality and availability (28, 30). Thus, the main factors for Sao Tome & Principe were identified since knowing each context-specific reality enables targeting and implementing the most proper evidence-based interventions (31).

The factors that drive the high perinatal mortality and ABO rates in this low-resource setting are mainly intrapartum factors. Having meconium-stained amniotic fluid, prolonged rupture of membranes (PROM), being transferred from another unit and instrumental-assisted vaginal delivery was found to increase the risk of stillbirth and neonatal death by 4– to 9–fold in this research.

In the case-control study, PROM and meconium-stained amniotic fluid were also found to be significantly associated with ABOs, reinforcing the role of intrapartum factors in peri-neonatal adverse outcomes. Additionally, twin pregnancies were also found to be significantly associated with ABOs in this research, similar to other studies (9, 32).

Having a high-risk pregnancy score was also an antepartum factor significantly associated with peri-neonatal mortality, consistent with other studies (33).

Comparing adolescent girls with older mothers, ABOs imputable to adolescent births were also related to intrapartum factors, namely, foetal distress with low first minute Apgar score <7 and performance of neonatal resuscitation manoeuvres. Additionally, compared to older mothers, teenage girls were likely to have a non-statistically significant threefold higher risk of having an obstructed labour. These are all amenable to modification with careful follow-up for adolescent pregnant girls during delivery and prompt referral for caesarean section in case of complications (40-42, 74). Other ABOs, such as asphyxia, risk for cerebral palsy, prematurity, neonatal sepsis and neonatal death, were identical between groups as well as maternal anaemia, mode of delivery or other obstetrical outcomes.

Globally, it is estimated that 15% of all pregnant women experience acute severe intrapartum complications that are responsible for half of all maternal deaths, 23% of neonatal deaths, and 32% of stillbirths annually (34), which is consistent with these findings. As an example, the PROM lasting more than 18 hours before labour overall rate in this study was 7.3%, which is in line with the estimated 5%-10% of all pregnancies in LLMICs (35, 36). The 17.3% rate of pregnancies with meconium-stained amniotic fluid is also consistent with other LLMICs studies (37).

These modifiable factors are also associated with healthcare service-related deficits in the country, namely, i) restricted access to advanced intrapartum equipment; ii) inadequate referral to clinical expertise; and iii) weak primary care that fails to facilitate a health system's response to sudden major obstetric complications with prompt referral to the HAM maternity unit.

Nevertheless, the country has already reached the major goal of having almost all pregnant women deliver in a healthcare facility (2). The delivery of the baby at home occurred only in 4.1% of adolescents and in 2.5% of the older woman group, which is a huge step to reduce perinatal and neonatal mortality. In STP, 93% of births are attended

by skilled health staff (2), a major accomplishment when compared to other Portuguese-speaking African countries, namely, Cape Verde with 91%, Equatorial Guinea with 68%, Angola with 50%, Mozambique with 54% and Guinea-Bissau with 45% (38).

However, Sao Tome & Principe, like other LLMICs, has an unproportionate doctor and midwives to prepartum women ratio (39). The end result is labour wards that are overcrowded, foetuses that are at a higher risk of complications (which may be recognized late), leading to unfavourable outcomes that have immeasurable financial, emotional, and physical impacts and short- and long-term consequences (40). Thus, it is worth noting the gap between the HAM maternity unit and other LLMIC maternity settings. HAM has a very reduce number of healthcare workforce with five obstetricians, 33 nurses and two general medical doctors for neonatology care and is responsible for 4500 births annually. This is compared to Nigeria, the University Teaching Hospital at Port Harcout, which has 24 obstetricians and 105 midwives for an average of 2500 deliveries per year, approximately half compared to HAM births (39, 41). Moreover, there is one anaesthesiologist in STP, meaning that even for life-saving situations, caesarean sections are not always feasible around the clock in the only unit in the country outfitted for it.

Therefore, to prevent ABOs, perinatal and neonatal mortality in STP, it is essential to have a complete team of healthcare workers with sufficient knowledge and skills to recognize, stabilize, and treat or refer pregnant women. It is also vital to scale-up healthcare facilities with technologies that allow early detection of intrapartum complications with timely intervention with essential lifesaving services available, such as being able to perform caesarean sections with having anaesthesiologists and obstetricians available around the clock (20, 21). There are also simple and cost-effective interventions that can have a huge impact and should be offered during childbirth within a very short time frame to all mothers-newborns in the country (42). The main recommendations will be discussed in section 4 of this Chapter.

Regarding antepartum factors, the case-control study identified that having fewer than eight ANC contacts was significantly associated with ABOs. This finding is similar to

reports from Ethiopia and other LLMICs, in which ABOs, especially PTB and LBW, were higher among mothers with limited antenatal care (ANC) visits (30, 43, 44).

ANC coverage in Sao Tome & Principe is a success compared to other SSA countries (45, 46). Almost 40% of pregnant women attend a minimum of eight ANC contacts, as endorsed by the 2016 WHO guidelines (47). Moreover, 85.1% of the participants had four or more contacts when, in the SSA region, only 62% are estimated to attend a maximum of four ANC contacts (45). Although ANC attendance is extremely high for a low-resource country such as STP, a first early booking in the first trimester was only achieved by half of the pregnant women enrolled. Nonetheless, the 51.7% rate of early ANC bookings is much higher than that in other LLMICs, such as Tanzania (12.4%), Nigeria (15.4%), Zambia (17%), and Ethiopia (27.5%) (48-51).

It was also identified that 94.5% of pregnant women received tetanus toxoid immunization. In comparison to other SSA settings, the good immunization rates of pregnant women in STP resulted in a huge positive impact on neonatal outcomes with a consistent neonatal tetanus elimination status in the country (52). Moreover, supporting the positive role of ANC services in health education, most participants in this research had appropriate knowledge in the identification of newborn danger signs, with the exception of adolescent mothers, who were significantly less likely to have this knowledge compared to their older counterparts.

All the above positive ANC factors promote the reduction of peri-neonatal complications in the country. STP already reached two out of four 90/90/80/80 targets and milestones for maternal and newborn health, with more than 90% women receiving the service of a skilled birth attendant at birth and more than 80% newborns obtaining first postnatal care within the first 24 hours after birth (2). However, it still misses the target of 90% coverage of ANC 4 or more contacts and the 80% availability at the districts of critical emergency care for women with complications and for small and sick newborns, as previously discussed.

When assessing ANC screenings tests per pregnant woman, there was a huge gap in ANC screening test completion amongst the participants. This is an important public health problem since missing out on these ANC evidence-based screenings risks women missing out on the prevention or treatment of maternal anaemia, bacteriuria, reduction of the risk of LBW neonates, PTB, neonatal sepsis, and stillbirths (47, 53, 54).

Only 5% (22 pregnant women out of 445) had completed all the following five essential interventions: i) attended ANC clinic eight or more times, ii) first booking before the 12th gestational week, iii) had at least one ultrasound, iv) had at least two urine tests, and v) performed no less than two haemoglobin tests.

Amongst the women with a minimum of four contacts and ANC screening completion (one ultrasound plus one haemoglobin plus one urine test), a high rate of 52.1% had only a partial ANC service utilization, indicating that most women had not undergone one obstetric ultrasound, urine and haemoglobin test throughout the pregnancy.

The study of the determinants for an adequate ANC service utilization allowed to identify that maternal age greater than twenty years (sociodemographic characteristic), urban residence (community level characteristics) and a planned pregnancy (pregnancy-related characteristic) were found to be significantly associated with adequate ANC utilization. Highlighting, once more, the vulnerability of adolescent pregnant girls, pregnant women from rural areas and those who had an unplanned pregnancy in assuring high-quality ANC service utilization. This poor ANC healthcare utilization is a well-recognized international public health challenge, especially in low-resource countries, with prejudice of the health of the expectant mother and the unborn child (55, 56).

The gaps in ANC, beyond the number of contacts: identification of screenings performed, maternal problems detected, and treatments provided to pregnant women during ANC to improve perinatal and neonatal outcomes in STP were then analysed. An ANC screening test absence between 24% and 41% was found and financial constraints were registered in 36% of ANC pregnancy cards as the motive for not completing screenings. Missed screenings were found for HIV in 4.5% of pregnant women, syphilis in 8.8%, HBV in

39.3%, malaria in 25.8%, haemoglobin in 24.5%, blood glucose in 45.4%, urine in 29.7%, coproparasitological exams in 27.8% and obstetric ultrasound in 41.1%. Moreover, missed ANC treatments were up to 50%.

In STP, most ANC screenings are paid out-of-pocket, a huge cost for pregnant women and an important drawback. A significant number of women do not have the financial resources needed to pay approximately 17 USD for routine ANC screenings when living on a budget of 1.40 USD per day (57). Furthermore, approximately 70% of women in this study were not economically independent since they had no job, which is consistent with published data for STP (2). In STP, women are mostly unemployed and constitute most of the inactive population (57). Poverty affects relatively more women (71.3%) than men (63.4%) and seems to be negatively correlated with the level of education with an impact on ANC utilization and screening tests completion (58).

Regarding maternal antenatal problems, the most common were i) intestinal parasitic infections, ii) bacteriuria, iii) maternal anaemia, iv) sickle cell solubility test positive and v) RhD-negative phenotype.

It should be emphasized that maternal anaemia and bacteriuria are important public health problems associated with key neonatal complications amenable to prevention (47, 53-55). Moreover, since one-third of pregnant women enrolled did not even have one screening done throughout all pregnancy, it is predictable that these maternal problems assume even higher rates. Notwithstanding this limitation, bacteriuria was identified in 43.2%, more than double the range of 2% to 16.43% usually reported for pregnant women in SSA countries (59, 60). Anaemia was diagnosed in 37% of pregnant women, similar to the 41.8% overall prevalence of maternal anaemia in Africa (54). Thus, anaemia and bacteriuria during pregnancy should be urgently addressed in STP to prevent related complications such as intrauterine growth retardation, PTB, LBW, and stillbirths (54).

There was an overall intestinal parasitic infection (IPI) prevalence of 58.2%, mainly due to soil-transmitted helminths (STHs) with a 55.9% rate identified. Nearby countries have lower rates, namely, Ghana with 23.0% (61) and Nigeria with 20.8% (62), but there are

some LLMICs, for example, Ethiopia, that have higher IPI rates (70.6%) among pregnant women (63). The predominant parasite species identified were 90.9% *Ascaris lumbricoides*, 13.8% *Trichuris trichiura*, 3% *Schistossoma intercalatum,* and 1.9% *Entamoeba histolytica.* Polyparasitism was observed in 11.9%.

IPI was significantly associated among pregnant women with primary education, unemployed, and a parity of five or above, all linked to poverty-related factors equally described for other LLMIC settings (61-64). These findings suggest a child-driven intrafamily transmission of parasites in STP since grand multiparous women have more children, which is in accordance with previous studies that described a high burden of IPI among children in STP (65). The high rates of ascariasis and trichuriasis show that transmission occurs due to soil and domestic water supply with faecal pollution around homes with poor sanitation (64). Regarding IPI treatment, anthelmintics were prescribed to 23% of IPI-pregnant women. Notably, *Schistossoma intercalatum* (n=11) and *Entamoeba histolytica* (n=7) infections were not adequately treated.

Adverse obstetric and perinatal outcomes, such as maternal anaemia, PTB, LBW and stillbirths, were analysed by comparing pregnant women with no-IPI and those with monoparasitic IPI and polyparasitic IPI. Additionally, ABOs were also compared between the no-IPI and IPI subgroups, namely, helminthiasis (n=162), schistosomiasis (n=11) and amebiasis (n=7). No difference was found for any of the abovementioned comparisons. In contrast, babies from helminthic-infected-mothers tended to have fewer low-birth-weights than noninfected counterparts. The lack of adverse outcomes can be related to the predominant type – *Ascaris lumbricoides* – a low pathogenicity parasite rarely associated with peri-neonatal complications (64). In this setting, the decision to treat should be based on the impact of the IPI on the pregnant-foetus on an individual-basis.

From the additional ANC maternal problems detected, this research identified a 13% rate of sickle cell disease or trait (66), highlighting a crucial need to understand the real burden of this condition in the country since administration of neonatal early prophylaxis and proper disease follow-up considerably reduces sickle cell complications.

The risk for RhD alloimmunization was also identified, as the Rhesus factor was negative in 5.8% of pregnant women. A similar frequency of the RhD-negative phenotype was published in Nigeria (4.4%), Kenya (3.9%), Guinea (4.1%) and Cameroon (2.4%) [54]. However, it is much lower than the 14% and above prevalence of the Rh-negative phenotype among Caucasians (67). This risk of alloimmunization to RhD can cause ABOs and compromise obstetric care in STP due to the unaffordability of anti-D immunoglobulin in the country.

The findings of this research support the success of the triple elimination of HIV, syphilis, and hepatitis B already acknowledged for Sao Tome & Principe (52, 68). HIV was detected in less than one percent of our study participants, which is in accordance with published data (0.2%) for the country (68). Syphilis was diagnosed in 1%, lower than the estimated pooled prevalence of 2.87% for SSA (69). The percentage (less than 1%) of infected pregnant women who required penicillin for syphilis treatment in this study is identical to that published in other resource-constrained countries, such as South Africa and Angola (70, 71). Additionally, throughout this research, a total of 200 pregnant women received a point-of-care rapid test for the diagnosis of syphilis infection. A third generation screening rapid test was used by the researcher to verify if the results registered in the ANC pregnancy card for the syphilis rapid tests used in the country matched. The on-site-rapid syphilis test used - Hexagon Syphilis® - screening test for *T. pallidum* antibodies in whole blood (sensitivity: >99%, specificity: >99%), confirmed all the results documented in the ANC pregnancy card, validating the efficacy of the tests available at the country (72) (Appendix 9 and 14).

Less than five percent of women received a full intermittent preventive treatment during pregnancy with a sulfadoxine-pirymethamine dose (at least two doses) for malaria prevention, a proportion much inferior to that in Gabon, which reached up to 55% (73). In contrast, bed net coverage was higher for STP (85.3%) than the estimated coverage for Gabon (60%) (73). These results highlight that the use of full courses of intermittent preventive treatment in pregnancy with sulfadoxine-pirymethamine and bed net coverage is suboptimal and should be optimized to achieve the country´s goal of eradicating malaria by 2025.

Concerning associated factors, this research reinforces that early motherhood and adolescent pregnancy are major public health issues in STP, as 20.1% (95% CI 16,3- 23) were adolescent mothers. Pregnancy at a very early age (≤15) was experienced by 7.7%, a rate two times higher than the 3.5% published in Africa (74). Early childbearing (≥16 and ≤17) and late childbearing (≥18 and ≤19) were found in 43.3% and 49%, respectively. Additionally, child marriage was found in 25% of girls younger than 15 years and in 69% (≥16 and ≤17 years), a much higher rate than MICS reports of 5.4% and 28%, respectively (2).

The main characteristics found to be significantly associated with adolescent pregnancy were having a relationship with the baby´s father for a period of less than one year, lack of the baby´s father support, being single, and not using a contraceptive method. Regarding age-disparate sexual relationships, there is a huge age gap between sexual partners amongst adolescent girls as 62.5% have had relationships with men aged 20-29 and 9.6% with men aged 30-39 years old. This age gap, which is often up to fifteen years is a major concern, and for girls under 16 years old is considered sexual abuse in a number of societies, including in STP, and should be traced and prevented.

Most characteristics were linked to maternal factors and sociocultural aspects of the country. For instance, in STP, the main structure is the existence of nuclear-type families formed by the couple and their children (75, 76). Similar to other African societies, in STP, the concept of family is extended, including the father, wife (or other noncohabiting women), children and even consanguineous and nonconsanguineous relatives, based on the principle of collectivity and interdependence (75, 76). Moreover, many families in STP live in a kind of nonmarital union, which consists of regular or irregular visits by the male spouse to the women with whom he has had sexual relations, usually a young woman, from which there was a birth of a child (75, 76). This “polygamous” marital culture with a rate of 20% in the country promotes maternal single-parent households, conflict between mothers who share the same parent as their children, situations of poverty, and precarious housing without internal divisions, making it easier for children and young people to meet the intimate world of adult relationships very soon (2, 75, 76).

Moreover, the current trends, globally, are for having a growing proportion of single parenting households, and our finding is consistent with data for STP, with a 19% rate of single parenting, a high rate when compared to 3% of children in China, 4% in Nigeria and 5% in India (77). These findings also reflect two types of households in the country headed by women: those in which the man is absent but continues to play an important role in decision-making and sending support necessary for the maintenance of the aggregate, and those where the female is the sole parent and where there is no male support (absent), with the woman being responsible for generating income and making decisions, a huge burden for women living in STP, a country with important barriers to women´s well-being and economic independence (78). These two different models should be considered in healthcare policies and future studies.

Family planning services are the pillar of maternal, newborn and child health in Sao Tome & Principe, that mostly requires reinforcement and intervention. The lack of family planning services consequences were found for most study participants due to the i) high unplanned pregnancy rates (57.7% in adolescent girls and 55.8% in women >20 years), ii) early timing of pregnancies occurring in the first months of starting a relationship (59.5% for adolescent girls and 19.7% for women >20 years), iii) the low rates of previous contraceptive use (6.7% in adolescent girls and 28.7% in women >20 years), iv) the low rate of women willing to use future contraceptive methods to prevent a next pregnancy (49% in adolescent girls and 39.9% in women >20 years), v) choosing traditional contraceptives instead of modern ones (66.7% of adolescent girls and 19.4% of women >20 years), and 6) the women´s beliefs and generational mindset that “for every union a woman should offer a baby to her men” for social upgrading and financial support.

Unplanned pregnancies rates are a major problem in the country for most women regardless of their age and the probability of using contraception was found to rise with age, with a turning point at 34 years old. To highlight, the rates found for modern contraceptive use amongst adolescent and older women (6.7% in adolescent girls and 28.7% in women >20 years) are much lower than those recently published for other LLMICs (27.2% use for adolescents aged 15-19 years and 40.3% for women aged 20-34 years) (79).

Moreover, 30% of the adolescents enrolled were already in their second or third pregnancy before reaching 19 years old, and 13.4% had experienced a previous abortion, which is similar to other settings, translating, once more, a reflection of the lack of family planning in the country (80). In view of these results, it is crucial to take pragmatic steps to deliver proper reproductive and family planning services in STP.

As previously acknowledged, the UNICEF´s 2019 MICS for Sao Tome & Principe is the source most commonly used for neonatal and maternal health information (2). The latest MICS household survey included 664 women with a livebirth in the last two years of the survey. These women were asked to answer regarding events in the last two years, promoting a recall bias, that is a MICS well-documented limitation since it is a retrospective instead of real-time survey (2). Additionally, MICS surveys are one-offs or performed periodically with several year gaps, making it infeasible to track time trends in real time [51]. The research conducted had a similar number of MICS participants, but one of its main strengths, contrary to MICS, is that it was a real-time study, not vulnerable to recall bias since pregnancy information and childbirth data were directly collected from ANC pregnancy cards and from hospital obstetric and neonatal medical records. It is noteworthy that a total of 511 ANC pregnancy cards were reviewed, enabling the first analysis ever conducted on ANC practices and screenings among pregnant women in STP. The pregnant women´s profile (preconception and sociodemographic data) was reached through 518 structured face-to-face interviewer-administered questionnaires. This research is also the first one ever conducted in the country regarding childbirth and intrapartum factors at the HAM maternity unit. The review of obstetric records and medical charts from the 518 pregnant women enrolled have allowed the first analysis of major obstetric complications and main healthcare service-related problems in the country. Consequently, this research may be used as an input for comprehensive interventions to strengthen maternal and neonatal healthcare by tracking the quality of care at HAM and district health services, assessing the implementation of key interventions, and alerting referral processes.

Thus, it should be noted that worldwide sources provide estimations that can help create a picture of a neonatal health problem in a country, but they actually only provide a

blurred vision of the reality. Field studies, mainly in settings with a deficit of high-quality data due to limited surveillance systems, are a key strategy to achieve a specific-country characterization with data to perceive the real burden of the problem and all its main dimensions, as it was done through this research.

Moving beyond survival is also a cornerstone of this research. Ensuring women have a positive and fulfilling experience and wellness during pregnancy at the time of birth and during parenting and delivering healthy newborns that will thrive into the future generation is the ultimate aim for Sao Tome & Principe (82).

Therefore, the findings above discussed will undoubtedly provide additional evidence for intervention designers and policymakers to establish appropriate management protocols targeted to the specificities of this country, given that these findings were derived from reality and not from estimations.

In addition, there is an intrinsic value of health - a human right - and good maternal, neonatal and child health is not only an outcome of but also a foundation for country development (83).

Thus, investing in the Sao Tome & Principe maternal and child healthcare system is an excellent opportunity to contribute to saving newborn lives, preventing life-long disabilities, and accelerating the economic development and growth of this resource-constrained country: “Healthier and more educated, is wealthier!”

2 | Strengths and Limitations

Strengths

This hospital-based study was the first ever conducted in Sao Tome & Principe to analyse the causes and associated factors contributing to perinatal and neonatal morbidity and mortality in the country. This research focused on deaths but did not overlook the adverse birth outcomes and maternal, preconception, antepartum, intrapartum, postpartum and healthcare service-related associated factors. This might make the evaluation criteria more stringent and show a better picture of all pregnancy timeline events that are associated with perinatal and neonatal mortality and morbidity.

Moreover, in comparison with other studies from SSA settings, which mostly only analyse ANC utilization in terms of the number and timing of ANC contacts, this research included routine screenings, maternal diagnosis, and treatments to the number of contacts per pregnant woman.

Regarding intestinal parasitic infection, this might be the first description of *Schistosoma intercalatum* infection in pregnant women and associated neonatal outcomes, since other studies among pregnant women were not found in the literature.

Study design

The selection of cases and controls was based on the records of maternal and neonatal registers verified by the researcher, a paediatrician; therefore, it is less likely that this study has misclassification biases both in the exposure and case–control categories.

Regression models, a useful method for assessing the associations between neonatal mortality and various predictor variables, were used. From the several types of regression models, logistic regression was conducted, a type of statistical model that can be used to assess the relationship between a binary outcome (e.g., neonatal mortality vs. survival) and one or more predictor variables. Logistic regression models estimate the probability of the outcome occurring based on the values of the predictor variables.

Single researcher

This research was only possible thanks to the contribution and permanent availability and cooperation of the local collaborators (Appendix 12). Nonetheless, the main fieldwork tasks were conducted by a single researcher, which can be considered a major strength of this research.

There are several potential strengths, including: 1) consistency: a single researcher ensures that all data is collected in the same way, which can improve the reliability and validity of the study; 2) control: it is easier to maintain control over the data collection process and ensure that all necessary steps are taken; 3) efficiency: as it eliminates the need to coordinate and communicate with multiple individuals; 4) cost: can be more cost-effective than using multiple researchers, as it reduces the number of personnel needed; 5) expertise: if the researcher is highly skilled and experienced, he or she may be able to collect high-quality data more efficiently than a team of less experienced members; 6) confidentiality: may help to maintain confidentiality, as there are fewer people involved in the process.

Other strengths were previously discussed in the previous section and in the articles.

Limitations

There is a potential selection bias since only HAM births were included, disregarding the 20% proportion of women who deliver in community health facilities (2).

Another limitation was the small sample of the prospective cohort study (n=194) that aimed to identify factors associated with peri-neonatal mortality in Sao Tome & Principe (manuscript VIII Chapter 3). This was due to the percentage (334 maternal-neonate dyads) lost to follow-up, so it is not clear whether the findings are representative of the full sample. In terms of communication, 67.1% of women aged 15 to 49 years old have a mobile phone, and only 8.9% use it (2), which had an impact on this study follow-up. For future studies mobile phones are not the best tool to reach women. Taking that into account, these results (manuscript VIII Chapter 3) cannot be generalized (sample bias) since the real number of neonatal deaths after hospital discharge can be much higher than the rate found. Other limitations were described in each article/manuscript.

3 | Conclusions

Stillbirths and neonatal deaths were up to two times higher than the rates published for Sao Tome & Principe. One must therefore be aware that worldwide data sources on neonatal mortality rates for the SSA region provide only estimations with considerable methodological limitations. It is therefore critical to conduct field studies in countries without complete vital registration systems since there is no "one size fits all" in terms of perinatal and neonatal mortality reduction.

This research has provided answers to the triple *Wh* question: *"when, where and why"*? Most were stillbirths, thus, *when do they die?* during labour, *where?* in the maternity unit, and *why?* due to intrapartum complications and healthcare service-related factors.

Knowledge of the main modifiable factors and the context-specific reality of this country, enabled to prioritize the most high-impact solutions and cost-effective evidence-based interventions aimed at the reduction of preventable stillbirths and neonatal deaths. The findings advocate for quality care at birth, with a focus on the time of birth as it is the time when most deaths occur and when most lives can be saved, and long-term disabilities averted. Avoiding intrapartum complications and delays in prompt care was found to be a key strategy to be implemented and it requires responsive health systems that are equipped with lifesaving technologies and with healthcare professionals who can deliver high-quality and timely skilled care, such as emergency obstetric care around the clock and interventions for small and sick newborn babies.

Scaling-up intrapartum care, neonatal care and reproductive services are the most effective investments, with a quadruple return: saving newborns and their mothers, preventing stillbirths, reducing disabilities, and paving the way for optimal child development, wellbeing, and lifelong health in Sao Tome & Principe.

The present research may be a model for similar countries with limited political and administrative capacity for detecting the main gaps and flaws in neonatal health, enabling the design of country-specific target interventions and a better allocation of resources to where they are needed.

4 |Policy Implications

Long-term gain and benefits of this research relies on the prioritization of the most cost-effective interventions with immediate benefits on perinatal and neonatal mortality and adverse birth outcomes for this specific setting.

To ensure that the recommendations from this research are implemented in Sao Tome & Principe, the Ministry of Health (MoH), stakeholders and health professionals from central and district maternities need to be engaged with the findings and understand their consequences. Therefore, these results will be shared with health authorities and professionals through face-to-face meetings in the country. Additionally, these professionals will need to be included in the implementation of these recommendations, bringing their expertise and experience to support an improved healthcare practice, aimed at the reduction of preventable stillbirths and early neonatal deaths.

Providing technology and supplies without coordinated investment in the strengthening of health systems and training healthcare professionals will be insufficient for achieving peri-neonatal mortality reduction. Undoubtedly, for the maternal and child healthcare system to be improved in Sao Tome & Principe, the government needs to increase the quantity and training of health professionals at the HAM maternity and neonatal unit. The lack of a high-quality healthcare system is also a public health challenge impacting the country´s development, not only on high mortality rates, but also giving a negative contribution to the country's tourist attractiveness, negative impact on the productivity of the various economic sectors and implications in terms of health expenditure (52).

According to our research, the priority is to prevent stillbirths through proper foetal surveillance, therefore, measures such as, the implementation of simple techniques in all maternity units, namely foetal heart rate monitoring and to provide algorithms to deliver prompt interventions when needed are essential. To target the modifiable risk factors identified through this research, four areas of care should be prioritized: intrapartum care, neonatal care, family planning care and antenatal care, the "**Four Care Goals**":

Intrapartum Care goal | To reduce intrapartum complications and healthcare service-related factors by:

i. making efforts to retain and recruit more skilled health-care workers (SDG target 3.c.1), reinforce facility infrastructure and supplies, develop and strengthen referral networks, scale up intrapartum monitoring, offer opportune intervention in case of complications and improve the availability and quality of emergency obstetric care;

ii. offering assisted delivery around the clock;

iii. prompting recognition and early referrals of pregnant women with complications from district maternities to the HAM maternity to avoid delays in prompt intrapartum care. For example, by training community-based health midwives in using portable point-of-care ultrasound technology during the third trimester (84, 85);

v. engaging nurses to use the WHO tool "Safe Childbirth Checklist" in Sao Tome & Principe through on-hand courses (41, 86);

vi. promoting foetal heart monitorization by making cardiotocography (CTG) available at all country maternity units and to develop national protocols on indications of CTG, intermittent auscultation and prompt recognition of danger signs and foetal distress (40);

vii. addressing within-country disparities. Maternity units furthest away from the HAM maternity unit should be prioritized for training and equipment to help detect complications in case of adverse weather conditions or lack of flights which can cause delays for women to access HAM.

(Further details regarding abovementioned interventions are described in section 3.8. Part II Chapter 1)

Neonatal Care goal | To scale-up neonatal care for small and sick newborns by:

i. implementing Level-2 inpatient newborn care at HAM with respiratory support through bubble continuous positive airway pressure (CPAP), as evidence has shown that adding this can reduce neonatal mortality by 50% (section 1.3.4) (20, 21, 42). The summary of the project proposal can be accessed in Appendix 2.

ii. introducing Kangaroo Mother Care (23). The summary of the project proposal can be found in Appendix 3.

iii. creating a new protocol for neonatal postpartum care reinforcement promoting mother and newborn early skin-to-skin contact and initiating breastfeeding in the first hour of life (87);

iv. providing mandatory refresher courses on neonatal resuscitation skills with hands-on training, and practical mentoring built on complementary curricula (88);

v. establishing train-the-trainer programme that will help to scale up training for new staff and the implementation of skills acquired in the district facilities in-country.

vi. promoting structured training in the national nursing institute (Instituto Superior de Ciências da Saúde Victor Sá Machado) leading to a neonatal nurse specialist degree in the country.

(Further details regarding abovementioned interventions are described in section 3.9. Part II Chapter 1)

Family Planning Care goal | To reduce the number of adolescent pregnancies (SDG target 3.7.2.) and to promote family planning services (SDG target 3.7.1) by:

i. promoting early engagement in family planning services and choosing modern contraceptive methods for women of reproductive age by raising awareness of its importance through television and other media programmes.

ii. preventing unwanted pregnancies with a special focus on targeting women with non-modifiable risk factors, such as early and advanced maternal age, chronic medical conditions and grandmultiparae (28, 89);

iii. involving men in planning the pregnancy and to use modern contraceptive methods by developing messages that specifically target men, as they are key opinion leaders and decision makers in the country (90).

iv. postponing adolescent childbearing using schools to promote both empowerment and awareness of girls and, at the same time, reinforce the role in fatherhood and shared responsibilities of boys (91). Focusing on its major underlying factors - debut of first sex, marriage, and effective modern contraceptive use - along with the social, cultural, and economic background surrounding these behaviours, girls' education and gender inequality are remarkable (92, 93).

v. opening debate in society to improve the awareness of the risks of age-disparate sexual relationships and the ways to minimise them.

vi. motivating healthcare services in STP to actively follow-up high-risk adolescent girls to prevent further early pregnancies and complications.

vii. assuring that women at reproductive age initiate supplementation before conception, since major malformations identified through our research were amenable to prevention. (Further details regarding abovementioned interventions are described in section 3.10. and 3.11. Part II Chapter 1)

Antenatal Care goal | To improve the quality of ANC services in the country by:

i. offering a complete free maternal ANC healthcare package, covering all screenings (SDG target 1.3.1) in view of achieving universal screening tests completion (94);

ii. training health professionals on prescription of intestinal parasitic infections, and referring and following up for adequate treatment in the postpartum period all pregnant women refusing treatment during the pregnancy period;

iii. shifting iron and folic acid supplementation to ANC micronutrient supplementation (MMS) as an option with broader advantages in reducing adverse birth outcomes (95);

iv. introducing sickle cell disease (SCD) neonatal screening programs through novel, rapid, inexpensive, and sensitive immunoassay-based point-of-care test kits that have high sensitivity and specificity in SSA settings (96, 97). Meanwhile, all pregnant women with a positive test for the disease or trait should be followed-up, and their newborns should be tested in a resourced-SCD laboratory in a nearby country through a dried blood sample, for neonatal early prophylaxis and follow-up to reduce disease complications;

v. eliminating ANC Widal tests. The lack of efficiency of the Widal test in diagnosing typhoid fever without other confirmatory tests is not of diagnostic value (98); thus, it should not be performed as a routine antenatal care practice in STP;

vi. improving data registration on ANC pregnancy cards by engaging nurses to understand the key value of quality data. Moreover, height, weight, and body mass index are not registered during ANC visits in STP, as it is not mandatory according to the WHO (47), but this could be reviewed for this setting.

(Further details regarding abovementioned interventions are described in section 2.3.1. Part I and 3.10. Part II Chapter 1)

The four abovementioned care goals recommendations need to be complemented by the following:

1) establishing a complete and fully functional civil registration and vital statistics system.

2) developing ongoing expertise, training and building capacity in obstetric and neonatal care with a “north-south” mentorship programme between Portugal clinicians and STP clinicians;

3) strengthening research and conduct further studies;

4) promoting international cooperation aiming to reduce preventable stillbirths, perinatal and neonatal deaths and adverse neonatal outcomes;

5) scaling up the WHO “sanitation ladder” toward better health for all in the country.

As a result, the greatest investment in interventions and programs that improve neonatal outcomes will benefit individuals across their life course and provide substantial population-level human capital returns for Sao Tome & Principe.

5 | Future studies_ Filling the gap

This hospital-based study provided many insights; nonetheless, several questions remained unanswered or emerged throughout this research. Prioritizing studies into specific causes of neonatal mortality in STP is still needed. Some proposals for future studies were already mentioned in the articles/manuscripts.

To fill the gap in neonatal health in STP, the following questions prevailed, which can be answered through further research:

1| To fill the gap in mothers´ care and practices of their newborns, the researcher is planning a prospective study to be conducted at community health centres for mothers of babies less than three months of age (Appendix X).

2| Studies assessing midwives' utilization of partograph and its determinants in the HAM maternity unit and district maternities of the country can bring great value to the design of appropriate intervention strategies to scale-up the quality of maternity care.

3| Research into women's perception and satisfaction with ANC and HAM maternity unit services will be extremely important, as the researcher perceived a negative and fearful sensation by some mothers regarding delivery at HAM. Moreover, some mothers reported obstetric violence at the time of delivery.

4| This research identified that 30.1% of women had experienced a previous abortion. Moreover, most abortions are underreported, and causes for spontaneous abortions are unknown in STP. The ideal future study to document pregnancy losses (early and late) at the population level will be to identify women before conception and follow them to determine pregnancy outcomes (89). Understanding the main causes of spontaneous abortions would also draw attention to underlying infectious or malformation origins amenable to prevention, reducing perinatal mortality rates in the country.

Additionally, there is the need to fill the knowledge gap in the following fields identified through this research findings:

Neonatal sepsis: To identify leading neonatal pathogens, namely, *Klebsiella pneumonia* or HIC-pattern with GBS and *E. coli* and the antimicrobial resistance pattern.

Group B Streptococcus: identification of GBS vertical transmission rate in STP.

TORCH infection: suspected cases should be considered for clinical and socioepidemiological characterization and follow-up. A spot of blood from a heel stick of these infants could be placed on filter paper for a dried blood spot and sent to an international reference center for diagnostic purposes.

S. interacalatum and E. *histolytic* infection impact: larger studies are needed to establish any causal nature of observed associations and to explore the impact of these IPIs among pregnant women.

Asymptomatic bacteriuria: future studies are also needed to determine the uropathogens and their sensitivity patterns.

Sickle Cell Disease: to determine the incidence of sickle cell disease in Sao Tome & Principe. Given that early diagnosis of the disease improves child survival, efforts should be made to study the real disease burden in the country.

Haemolytic Disease of Newborn: identification of the burden of this disease in STP.

Foetal alcohol syndrome: future studies on the incidence of foetal alcohol syndrome, alcohol-related neurodevelopmental disorder, and alcohol-related birth defects in Sao Tome & Principe are needed. Alcohol consumption among women of childbearing age in STP is estimated to be high (2), and pregnancy consumption and outcomes/impact (short- and long-term) on neonatal health should be clarified.

"Simple people, doing small things, in unimportant places,

achieve extraordinary changes."

African Proverb

We all live in the 21st century but we do not all belong to the 21st century high-quality healthcare, lifestyle, well-being and education.

No newborn babies should die from preventable causes in the 21st century, regardless of where they are born, and every step should be taken to end these deaths in this country.

These “simple” midwives and doctors, working every day in “small things” in an “unimportant place” - with the right tools and strategies - can surely achieve extraordinary changes for babies born in Sao Tome & Principe.

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APPENDIXES |

APPENDIX 1 | Best presenters of GLOBEHEAL 2022

Available at: https://www.ihmt.unl.pt/estudante-de-doutoramento-do-ihmt-nova-vence-melhor-comunicacao-oral-no-globeheal-2022/

Estudante de doutoramento do IHMT-NOVA vence melhor comunicação oral no GlobHeal 2022

9 MARÇO, 2022



Alexandra Vasconcelos, estudante do Doutoramento de Medicina Tropical, no Instituto de Higiene e Medicina Tropical da Universidade Nova de Lisboa (IHMT-NOVA), é uma das vencedoras da **melhor comunicação oral** intitulada "Antenatal care in São Tomé e Príncipe: beyond the number of visits" no GlobHeal 2022 – 5ª Congresso Global de Saúde Pública – Futuro da Saúde Global num Mundo em Mudança, que decorreu nos dias 24 e 25 fevereiro.

A médica portuguesa apresentou ainda mais duas comunicações orais no âmbito da tese de doutoramento sobre morbilidade e mortalidade que está a desenvolver no IHMT-NOVA: "Pregnant Women Profile: Are there differences in antenatal care in São Tomé e Príncipe?" e "Adolescent Pregnancy in São Tomé e Príncipe: Are there different obstetric and perinatal outcomes?"



O GlobHeal 2022 – 5ª Congresso Global de Saúde Pública contou com mais de 350 participantes de mais de 45 países. Saiba mais aqui.

Veja aqui o vídeo dos vencedores dos melhores posters e comunicações orais

APPENDIX 2 | Positive Air

Proposal submitted to 2022 Children's Prize

Available from: https://www.childrensprize.org/

One of the finalists (total of 200 applications from 45 countries)

Proposal for an intervention in the Neonatal Care Unit in Sao Tome & Principe

2022 Children's Prize Round 2 Invitation
37 messages

Children's Prize <info@childrensprize.org> Thu, Sep 29, 2022 at 3:25 PM
To: alexandravasc@gmail.com

Dear Dr. Alexandra Vasconcelos,

Congratulations! You have been selected to participate in the 2022 Children's Prize Round 2 Prize Plan. We received over 200 applications from over 45 countries and only five percent of Round 1 applications were passed on to Round 2 this year. We urge this handful of excellent applicants to present a well structured project, plan, and impact estimate. Please note that an independent third party evaluator is required (see application for details).

To access the application, please login to the account used for your Round 1 application and select the Round 2 Prize Plan subcategory. While your Round 1 responses will be available to view, you will not be able to go back and edit them. Round 2 applications are due November 13th, 2022 at 23:59 EST. We will announce the 2022 winner of the $150,000 Children's Prize in December.

For more information about the prize, please visit www.childrensprize.org.
For any questions regarding the Round 2 Prize Plan, please contact info@childrensprize.org.

Best of luck!

--
Kristy Price
Children's Prize
FOUNDATION

2022 Children's Prize Finalist Announcement
3 messages

Children's Prize <info@childrensprize.org> Tue, Jan 17, 2023 at 6:11 PM
To: Alexandra Vasconcelos <alexandravasc@gmail.com>

Dear Dr. Alexandra Vasconcelos,

We would like to thank you again for applying to the 2022 Children's Prize. Your application was among the strongest we received, but after careful deliberation, the judging committee chose another project as this prize year's winner.

The judging committee took special interest in your application for its passionate and well-constructed intervention of implementing bubble CPAP in the neonatal care unit of Sao Tome & Principe. While the committee believed your intervention could be successfully executed, there were concerns regarding the novelty of the intervention compared to others.

All of our finalists presented strong plans with unique and appealing features, and we regret that we only have resources to grant one prize this year.

We are grateful for your time and effort in participating in this year's prize and wish you the best in your endeavors. We encourage you to apply again in future years.

Best regards,

--
Kristy Price
Children's Prize
FOUNDATION

Positive Air



Proposal by Alexandra Vasconcelos, Pediatrician, MD PhD student

Organization: GHTM – IHMT, UNL

Children´s Prize Foundation

Date: 30 july 2022

Setting: Neonatal Unit Care- Hospital Dr Ayres de Menezes, Sao Tome & Principe

Summarize your project in 140 characters

Implementation, training, and maintenance of bubble CPAP in the neonatal care unit of Sao Tome & Principe to improve outcomes for neonates with respiratory distress

Problem Background: Why is there a need for your project? 250 words

Sao Tome & Principe (STP) is one of the smallest African countries in which neonatal morbidity and mortality are perceived as a major problem, but a lack of evidenced-based interventions impedes tackle it down. Approximately 6,500 babies are born each year, although neonatal deaths are up to 22 per 1,000 and 22 per 1,000 are stillbirths. There is only one hospital in STP with EmONC capable of performing cesarean sections: Hospital Dr. Ayres de Menezes (HAM). During my PhD study at HAM, a variety of health-service-related factors and neonatal mortality

risk factors were identified, one of which was the lack of means to deal with the frequent neonatal respiratory distress syndrome (RDS). Newborns with RDS can be managed effectively with breathing support, such as mechanical ventilation or continuous positive airway pressure (CPAP), as well as surfactant replacement therapy. However, in STP, there are no neonatal intensive care units, or any facilities with mechanical ventilation, CPAP, or surfactant therapy to deal with RDS. An affordable and sustainable option is the use of bubble CPAP, which has been shown to be effective in supporting breathing in newborns and has a strong recommendation by the WHO. This strategy is of great importance in resource-constrained countries where mechanical ventilation is not available due to high costs, maintenance demands and the need for highly trained staff. Therefore, implementing bubble CPAP in the HAM neonatal care unit will be an important key strategy to reduce neonatal mortality and improve the healthcare of premature babies in STP.



Project and Intervention Description: what is the project you are proposing?

Positive **A**ir: Implementation, training, and maintenance of bubble CPAP for the Neonatal Unit Care (NUC) at HAM.

Setting: NCU receives high-risk babies delivered within the HAM and referrals from other basic health-facilities with a total capacity to admit six babies (six incubators). This unit is basic and able to manage simple neonatal complications. There are two pediatricians and no neonatologists in the country.

The health system strengthening will be implemented as follows:

1) Acquiring the Bubble CPAP devices and supplies (disposable nasal prongs, oxygen concentrators, etc.). Although less expensive than mechanical ventilation, conventional commercial bubble CPAP systems cost between US$6000 and 18,000.

2) Setup of six (6) Bubble CPAP

3) Training and staffing: to build momentum and motivation, an approach with a combination of external consultants (Portuguese neonatologists and neonatal nurses) with local clinicians and nurse staff will be used to provide training. Clinical mentorship and regular, interactive training will be put into practice.

4) Care of small and sick newborns: other basic interventions such as hypothermia prevention, feeding problems will also be addressed since bubble CPAP was not sufficient to reduce mortality, as a single intervention, if a preterm neonate was hypothermic in addition to RDS.

4) Caregivers: Information about bubble CPAP will be provided to all caregivers, and skin-to-skin contact will be promoted.

5) Maintenance and program sustainability: maintain CPAP training and maintenance sustainably

Provider-to-provider clinical mentorship models as well as affordability and cost-effectiveness of innovative bubble CPAP systems will be implemented throughout all intervention.

Estimate the number of children's lives that can be saved by your project (enter a number only, limit to 8 characters).

500

For the estimate you provided in the previous question, explain how you arrived at that specific number and include all assumptions made in your estimated calculation.

Preterm birth complications are a leading cause of neonatal death in STP. Preterm newborns often have underdeveloped respiratory systems, with more than 50% of infants born before 31 weeks gestation developing respiratory distress syndrome (RDS). Additionally, perinatal asphyxia and other neonatal complications are associated with RDS and a high-risk of death.

Therefore, with “Positive Air” project with bubble CPAP, approximately 30-40 premature (<31 GA) newborn lives could be saved each year. Additionally, another 40-50 newborns (NB) with RDS would be treated with Buble CPAP.

Annual birth cohort: 6.500

Neonatal mortality rate: 22 per 1.000 = 143 NB deaths/year

Causes of neonatal mortality (UNICEF MICS): prematurity in 36%, intrapartum conditions in 28%, therefore, approximately 53 NB and 40 NB deaths annually could be prevented.

Total: 93-100 NB saved/per year with a reduction to less than 12 deaths per 1.000 live NB.

For the two-year project duration: approximately 200 newborns could be saved and the SDG (target 3.1) of no more than 12 neonatal deaths would be achieved in STP.

5-year follow-up: 500 NB lives saved

For your estimate of lives saved, describe how you plan to verify that the expected impact you have predicted has actually occurred?

One approach will be to introduce a PhD student from GHTM-IHMT, Universidade Nova de Lisboa, to perform a project on this intervention impact.

A second approach would be the submission of reports throughout the field project implementation.

Another approach is having a third-party independent evaluator to assess the outcomes.



Please provide a small table of authorities (ie references) for the primary evidence-based claims upon which the rationale for your proposal rests.

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8. Zubizarreta JR, Lorch SA, et al. Effect of prophylactic CPAP in very low birth weight infants in South America. J Perinatol 2016;36:629–34.

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13. Kinshella W, Walker R.,*et al.* Barriers and facilitators to implementing bubble CPAP to improve neonatal health in sub-Saharan Africa: a systematic review. *Public Health Rev* **41,** 6 (2020). https://doi.org/10.1186/s40985-020-00124

APPLICANT

What have you done in the past that would lead us to believe that your project plan, if awarded the prize, would be successful?
0 / 420 words

I am a Portuguese pediatrician with 14 years of short- and long- missions in Sao Tome & Principe, with a postgraduation in Tropical Medicine from London School and Tropical Medicine (first East-African Course in Uganda and Tanzania), and I am about to finish my PhD thesis on neonatal mortality in STP. Nothing had more impact on me, than the experience of working as a resident in an African hospital and rural districts back in 2008. After facing the challenges of such difficult diagnosis and dealing with my own impotence considering so many children's deaths that could have been prevented if only there were more resources, I simply decided to devote my path to changing this. In 2010, my second mission in STP, was all about training the midwives to follow the basic steps and the WHO algorithm in newborn resuscitation. The field of work consisted of a theoretical workshop and the practical training of a total of 100 midwives, as well as equipping the countries' seven maternity units with basic neonatal material. Accordingly, to STP´s health authorities this intervention was a huge success. Afterwards

we were awarded by the Portuguese Estefania Pediatric Hospital. Between 2010 and 2013, I was in charge of some other short-missions in several fields such as trauma, respiratory infections, and adolescent sexual health. In 2012, I went to Bissau to implement the Integrated Mother and Child Health Programme (PIMI). In recent years, my PhD project: Why, When and Where do newborns not only get sick but also die in Sao Tome & Principe? enabled me to analyze causes and risk factors contributing to peri-neonatal morbidity and mortality in this country. The sum of all these activities made me a pediatrician with experience in child global health able 1) to build proposals for the maternal-child programme for the health system and interact with diverse stakeholders, 2) to have the know-how in the design and mainly in the implementation of project plans, 3) to manage and monitor the projects in and for low-income-countries, and 4) to have the ability to work in partnership with all children, mothers and families, health professionals, agencies, communities and government.

My ultimate goal is to be of use and to help improve our children's lives. I deeply believe my motivation added to my solid expertise makes me a candidate to successfully implement the **P**ositive **A**ir in STP if the Children´s Prize Fund gives me the chance and the great honor to be awarded to complete this mission.

APPENDIX 3 | Kangaroo Mother Care and premature care improvement

Proposal for an intervention in the Neonatal Care Unit in Sao Tome & Principe

Submitted to funding by Camões Instituto da Cooperação e da Língua Portuguesa – Ministério dos Negócios Estrangeiros

PROJETO

Ficha de identificação Sumária

A. Título do Projeto: (O título deve traduzir de forma sintética o tema central do projeto proposto)	**MELHORIA DOS CUIDADOS A PREMATUROS: MÉTODO CANGURU**
B. Entidade Proponente (Indicar o nome, a sigla, o endereço completo, telefone, fax, correio eletrónico, estatuto jurídico e principais doadores da entidade proponente do projeto, bem como os contactos dos responsáveis do projeto/interlocutores)	Universidade NOVA de Lisboa (UNL), Instituto de Higiene e Medicina Tropical (IHMT), Global Health Tropical Medicine (GHTM) Responsável pelo projeto: Alexandra de Castro Vasconcelos (AV) Email: alexandravasc@gmail.com
C. País/Região: (Localização concreta. Por exemplo, Angola, Província de Luanda, Município de Viana)	São Tomé e Príncipe (STP), São Tomé Hospital Dr. Ayres de Menezes (HAM) – Unidade de Cuidados Neonatais (UCN)
D. ODS e METAS: (Identificar o objetivo(s) de Desenvolvimento Sustentável e respetiva(s) meta(s) – ver anexo III)	**ODS 3** _ Saúde de Qualidade **Meta 3.2.2** Acabar com as mortes evitáveis de recém-nascidos com a redução da mortalidade neonatal para ≤12 mortes neonatais por 1.000 nados-vivos até 2030. **Meta 3.12** Formação e capacitação das enfermeiras da UCN em cuidados aos prematuros. O presente financiamento permitirá introduzir no país, de

	forma célere, uma importante estratégia de alto impacto na redução da mortalidade do recém-nascido prematuro – o Método de Canguru, que foi previamente identificada como inexistente no país.
E. Setor: (Identificar o Setor e Subsetor de atuação em que o projeto se insere. Por exemplo, setor social, subsetor saúde, área dos cuidados materno-infantis)	Sector da Saúde – Cuidados Materno-Infantis
F. Objetivo da Intervenção (Indicar de forma sucinta o objetivo principal que o programa/projeto pretende atingir)	Objetivo principal é o de contribuir para a melhoria da assistência ao recém-nascido prematuro com: 1) impacto na redução da taxa de mortalidade neonatal 2) otimização do bem-estar e saúde do prematuro 3) maior ganho ponderal 4) alta mais precoce Formação (Unidade Cuidados Neonatais): • Médicos • Enfermeiros • Mães dos RNs prematuros Incluindo "Formação de Formadores" (equipa de médico e enfermeiros). O projeto visa a capacitação adicional e formação das enfermeiras da UCN sobre os cuidados específicos ao prematuro (colheita de sangue, colocação de acessos intravenosos, administração de terapêuticas) e aplicação do Método Canguru, com o apoio à definição do seu protocolo de funcionamento e assessoria à sua organização e implementação. Formação dos médicos nas normas e protocolos em vigor para o cuidado do recém-nascido prematuro e redução das complicações a curto e a longo prazo. Apoio suplementar e treino da equipa de enfermagem nacional em técnicas de administração de injetáveis, alimentação por sonda nasogástrica, cuidados da pele e otimização das incubadoras ao cuidado do recém-nascido prematuro. Adquirir dois monitores ApneBoot para prevenção das apneias do prematuro.

G. Marcador Ambiente e Marcador do Rio (Identificar quais os marcadores a aplicar)	
H. Capacitação (Indicar se envolve reforço de capacidades)	**Sim**
I. Tecnologia (Indicar se envolve transferência e /ou desenvolvimento)	**Não**
J. Grupo-Alvo (Identificar os beneficiários diretos. Por exemplo: 100 mulheres, utentes de um centro de saúde YXZ, necessitando de apoio neonatal para recém-nascidos prematuros)	Beneficiários diretos: 150 prematuros internados na Unidade de Cuidados Neonatais (UCN) da Maternidade do HAM (média anual) (anexo V) 30 enfermeiras 2 dois médicos da UCN que beneficiarão de formação, capacitação e assistência técnica aos cuidados ao prematuro bem como assegurar a implementação do método canguru. “Formação de Formadores”: um médico e três enfermeiros receberão orientação complementar de todas as intervenções. Pretende-se formar uma equipa nacional habilitada e responsável pela formação contínua no país sobre o MC e cuidados aos prematuros após o término desta intervenção. Beneficiários finais do projeto: todos os prematuros e/ou com baixo peso admitidos na UCN a partir de julho de 2023

K. Entidade Executora (Indicar o nome, a sigla, o endereço completo, telefone, fax, correio eletrónico, NIF e detalhes bancários da entidade executora do projeto – entidade bancária, balcão, titular, n.º conta e NIB – bem como os contactos dos responsáveis do projeto/interlocutores)	Universidade Nova de Lisboa (UNL) – Instituto de Higiene e Medicina Tropical (IHMT) Rua da Junqueira, 100 _ 1349-008 Lisboa Telefone: 213652600 _ Fax: 213632105 Email: financeira.ihmthmt.unl.pt NIF 501559094 IBAN: PT50078101120000000454516 Instituição bancária: Agência de Gestão da tesouraria e da Dívida Pública – IGCP, EPE Responsável pelo projeto: Alexandra de Castro Vasconcelos Email: alexandravasc@gmail.com
L. Duração e calendário previsto (Indicar a data prevista de início de fim da intervenção bem como as diferentes fases da mesma, em meses)	2024-2025 (12 meses: maio 2024 a maio 2025)
M. Custo do projeto (Indicar o custo total do projeto em euros)	
N. Plano de Financiamento (Indicar as entidades financiadoras e o montante da sua participação em valor absoluto em euros e o seu valor relativo em %)	Projeto a ser financiado exclusivamente pelo Camões, I.P._ 100% Este projeto vem na sequência da investigação de doutoramento de AV intitulada: *When, Where and Why do newborns not only get sick but also die in Sao Tome & Principe?* *Analysis of causes and risk factors contributing to perinatal and neonatal morbidity and mortality in a developing country – a case-control study* Investigação que recebeu financiamento através de bolsa individual de doutoramento da FCT (AV) SFRH/BD/117037/2009 e que já terminou atendendo que a proponente está na fase de entrega da dissertação.

APPENDIX 4 | Newborns admission at Neonatal Care Unit at Hospital Dr. Ayres de Menezes: a retrospective study

Newborns admission at Neonatal Care Unit at Hospital Dr. Ayres de Menezes: a retrospective study article for studying neonatal deaths at NCU is being prepared.

Meanwhile the following abstracted was submitted and will be presented as a poster communication at 2023 ESPID.

Neonatal sepsis in a resource-constrained country without blood cultures will be presented at ESPID 2023 (41st Annual Meeting of the European Society for Paediatric Infectious Diseases), Lisbon 8-14th May 2023.

TITLE: Neonatal sepsis in a resource-constrained country without blood cultures

AUTHORS: Joana Vasconcelos1, Beatriz Vaz1, Swasillanne Sousa2, Marta Alves3, Ana Luísa Papoila3, Alexandra Vasconcelos4

Background: Sepsis is one of the foremost reasons for neonatal death in Sub-Saharan Africa (SSA). Sao Tome & Principe (STP) is a resource-constrained SSA country. Probable early-onset neonatal sepsis (EOS) in STP is defined as having an intrapartum infectious risk and clinical suspicion, without gold-standard culture diagnosis. In this study we aimed to describe probable EOS and infectious risk among newborns admitted at the only neonatal care unit (NCU) in STP. This is the first study ever conducted at this NCU.

Methods: Retrospective chart review of neonatal admissions at NCU in Hospital Dr. Ayres de Menezes in STP, between October 2021-October 2022.

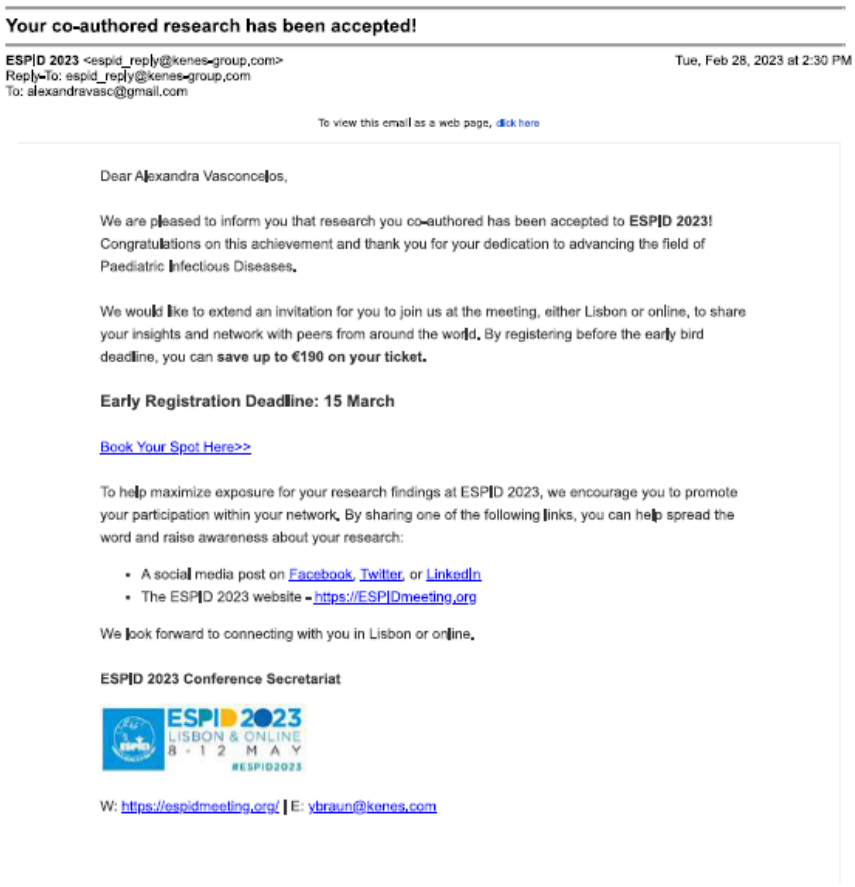
Results: Of 948 neonatal admissions, 53.2% were male, 5.8% twins, 73% birthweight ≥2500g-<4000g, 16.2% premature (1.7% EPT, 3.8% VPT, 10.7% LPT). Most common reasons for admission were: 1) infectious risk with meconium-stained amniotic fluid (25.2%), 2) probable EOS (17.1%), 3) prematurity-complications (9.8%), asphyxia (6.1%), congenital anomalies (3.5%), HIV-MTCT treatment (3.1%). The average length of stay was 5.5 days (SD 7.8). The overall mortality rate was 6% (57), with 20% (200) missing discharge information. Infectious risk neonates (239) characteristics: 50.6% female, mean birthweight 3146g and GA 39.53 weeks, mean maternal age was 26, 23.4% caesarean, 12.6% foetal distress (1-min Apgar<7), 5.4%

clinical asphyxia (5-min Apgar<7), 98.7% completed 48h-antibiotic, 2 neonatal deaths (2.1%). Probable EOS neonates (162) characteristics: 55.6% male, mean maternal age 25.6, mean birthweight 3135g and GA 39.43, 99.4% completed 7/14 days empiric antibiotics, 4 neonatal deaths (2.5%).

Conclusions: The positive outcomes among EOS and infectious risk newborns of this study highlights that having a well-defined risk-based diagnosis strategy through identification of risk factors and timely initiation of antibiotics, can save many newborn's lives in limited resource-settings.

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4. Unidade de Clínica Tropical - Global Health and Tropical Medicine (GHTM), Instituto de Higiene e Medicina Tropical (IHMT), Universidade NOVA de Lisboa. Lisboa – Portugal



Your co-authored research has been accepted!

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Dear Alexandra Vasconcelos,

We are pleased to inform you that research you co-authored has been accepted to **ESP|D 2023!** Congratulations on this achievement and thank you for your dedication to advancing the field of Paediatric Infectious Diseases.

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APPENDIX 5 | Neonatal postpartum care: a prospective study

Proposal for a prospective study to be conducted in 2023.

Study: Postnatal care in Sao Tome & Principe

Supervisor: Alexandra de Castro Vasconcelos, Paediatrician, Global Health and Tropical Medicine, Instituto de Higiene e Medicina Tropical (IHMT)

Setting: PMI, Água Grande, postnatal visits

Date: October-November 2023

PROTOCOLO DE INVESTIGAÇÃO

1. FUNDAMENTOS DO ESTUDO

Segundo a Organização Mundial da Saúde (OMS), o período pós-natal começa uma hora após a terceira fase do trabalho de parto e vai até 42 dias após o parto. É neste período que ocorrem a maioria das mortes neonatais, sendo o período mais negligenciado para a prestação de cuidados de saúde de qualidade.

O período imediato do nascimento e as primeiras 24 horas podem ser da maior importância, sendo descritas como as "horas de ouro", uma vez que a maioria das mortes neonatais ocorridas após 48 horas de vida podem ser evitadas através de cuidados prestados imediatamente após o parto. Neste período podem também ocorrer complicações maternas, como hemorragia e sépsis, responsáveis por mais de um terço das mortes maternas em todo o mundo.

As orientações da OMS sobre cuidados pós-natais (CPN) abordam o momento, o número e o local dos contactos pós-natais e o conteúdo dos cuidados pós-natais para todas as mães, recém-nascidos e lactentes, durante as seis semanas após o nascimento e recomendam que as mulheres e os recém-nascidos sejam avaliados quanto a sinais de perigo.

De acordo com os dados da UNICEF do Multiple Indicator Cluster Surveys (MICS) de 2014 e de 2019 para São Tomé e Príncipe identificaram que mais de 90% dos recém-nascidos receberam a primeira consulta pós-natal nas primeiras 48 horas de vida. No entanto, a promoção do aleitamento materno na primeira hora de vida e o contacto pele-a-pele na primeira hora de vida entre mãe e recém-nascido foi identificado somente numa percentagem de 30%-35%. Identificando-se lacunas para melhoria dos cuidados ao recém-nascido.

Acrescentando-se que há dados importantes que não são incluídos, por norma, nos inquéritos da UNICEF-MICS. Nomeadamente, não há dados relativos à morbilidade neonatal, nomeadamente a percentagem de prematuros, asfixia perinatal, baixo peso ao nascer, sépsis e malformações congénitas.

Pelo que este estudo tem como objetivo identificar as características dos cuidados ao recém-nascido no período neonatal e principais morbilidades neonatais.

2. OBJETIVOS DA INVESTIGAÇÃO

Objetivos principais: Caracterizar os cuidados ao recém-nascido/lactentes no período pós-natal no Distrito de Água Grande em São Tomé. Identificar as principais causas de morbilidade do recém-nascido.

Objetivos secundários:

Caracterizar:

i. as condições sociodemográficas das mães e estrutura familiar.

ii. a história obstétrica materna, o parto e complicações maternas periparto e no pós-parto;

iii. o recém-nascido no período neonatal e o seu seguimento após a alta da maternidade, assim como os cuidados do cordão umbilical e tipo de amamentação.

3. DESENHO DO ESTUDO

Estudo observacional transversal

4. POPULAÇÃO E AMOSTRA A ESTUDAR

Recém-nascidos e lactentes até 3 meses de idade observados na consulta de enfermagem e/ou médica no PMI em outubro de 2023, residentes na área abrangida pela Água Grande.

5. DADOS A RECOLHER, MÉTODOS PARA OS OBTER, TRATAR E ANALISAR

Os dados a colher são:

- Sociodemográficos - idade materna, nível educacional materno e paterno, ocupação materna, estado civil materno, residência em meio urbano ou rural, existência de águas aprimoradas, saneamento básico.
- História obstétrica - índice obstétrico, espaçamento entre nascimentos, uso de métodos de planeamento familiar, gravidez planeada.
- Cuidados na gravidez - idade gestacional aos primeiros cuidados neonatais, número de consultas pré-natais, ecografia obstétrica, gravidez gemelar.
- Parto - tipo de parto e de assistência, complicações, local do parto, presença de membro da família.
- Características do recém-nascido - idade gestacional, sexo, peso ao nascimento, contacto pele a pele e amamentação na primeira hora de vida, banho adiado após as 24h de vida, complicações periparto, admissão em UCIN, necessidade de antibioterapia, mal-formações congénitas, sépsis neonatal, outras doenças, alta da maternidade após quantas horas de idade.
- Cuidados pós alta da maternidade - cumprimento do programa nacional de vacinação, número de consultas pós natais, periodicidade das consultas pós natais.

Recolha dos dados: Os dados irão ser recolhidos através de um questionário anónimo em formato google forms, com as informações fornecidas através de entrevistas com os tutores legais e consulta dos Boletins de Saúde Infantil e Juvenil.

A base de dados gerada em excel será depois analisada e os dados tratados recorrendo ao SPSS.

6. INDICADORES A PRODUZIR

Morbilidade neonatal (prematuridade, asfixia perinatal, malformações congénitas e outras doenças no período neonatal)

Número de consultas pós-natal.

7. DIVULGAÇÃO DOS RESULTADOS

Congresso Nacional de Pediatria SPP e eventual publicação científica.

8. CALENDÁRIO DO ESTUDO

Data prevista do início: 01 de outubro de 2023

Data prevista da conclusão: 31 de novembro de 2023

9. RECURSOS REQUERIDOS PARA A REALIZAÇÃO DO ESTUDO

Boletins de Saúde Infantil e Juvenil dos recém-nascidos e lactentes até 3 meses de idade (inclusive) e entrevistas com os tutores legais das crianças, que irão recorrer à consulta médica e/ou de enfermagem no PMI entre 01/10/2023 e 10/11/2023.

10. MEIOS PREVISTOS PARA CUMPRIR COM OS REQUISITOS ÉTICOS E LEGAIS

Para o presente estudo será necessário consentimento informado que será em formato digital com necessidade de atribuição de uma assinatura por parte do tutor legal da criança. (Anexo 2)

11. ENCARGOS FINANCEIROS PARA A DELEGACIA DE SAÚDE DE AGUA GRANDE

O presente estudo não terá quaisquer encargos.

APPENDIX 6 | How to read Chart 3 instructions

Source: United Nations Inter-agency Group for Child Mortality Estimation (2021)
Available at: http://childmortality.org.

The chart above can display all available source data on child mortality rates for a country along with the UN IGME estimate trend with uncertainty. The median UN IGME estimate is shown with a solid line (—), and the 90 per cent uncertainty interval is represented by the shaded area around the median line.

Source data can first be categorized according to the data collection method employed, indicated by the plotting symbol detailed in the 'Data collection method' legend below the chart. Data can originate from a vital or sample vital registration system, a survey or census collecting full birth histories, a survey or census collecting summary birth histories, a survey or census collecting information on household deaths (i.e. the number of deaths in the household usually in the preceding 12 months), or other collection methods such as life tables.

Source data can be further divided into data included in the estimation model and data excluded from the estimation model (note: data may be excluded for any one of several reasons including data quality or by rule—for example, indirect estimates from summary birth histories are not included when direct estimates from the full birth history from the same survey or census are available). Included data are shown with filled plotting symbols, e.g. ♦, and excluded data are shown with unfilled symbols, e.g. ◊.

Each data series (a 'data series' is all data points from one survey/census/vital registration system using the same data collection method) is distinguished by color, with its respective year and the calculation method listed in the legend. Data points from the same data series are connected by a line.

APPENDIX 7 | Intervention project of newborn resuscitation, support delivery and alarm signals in the first months of life in Sao Tome & Principe (2010-2012)

Available at:

https://www.bbc.co.uk/portugueseafrica/news/story/2010/07/printable/100719_stpportugalaidlv.shtml

BBC PARA AFRICA.com

19 Julho, 2010 - Publicado às 01:23 GMT

Artur Pinho
Correspondente da BBC em São Tomé

São Tomé procura diminuir morte de recém-nascidos

Em São Tomé e Príncipe, a asfixia é a causa principal de 19% das mortes de bebés recém-nascidos.

Estes números estão a preocupar as autoridades que, no quadro da cooperação com Portugal, através do projecto "Saúde para Todos" do Instituto Marques Vale Flor, receberam na última semana equipamentos para a reanimação neo-natal.

Esta doação agradou ao ministro são tomense da saúde. O aumento do número de mortes de bébés por asfixia durante o nascimento leva as autoridades sanitárias do país a reflectirem sobre o problema.

Esta situação colide com um dos objectivos de desenvolvimento do milénio que visa a diminuição da taxa de mortalidade de crianças com menos de cinco anos.

E um dos desafios é dotar as maternidades do país de equipamentos apropriados para o efeito.

Para tal, as autoridades contam com a parceria do Instituto de Vale Flor de Portugal, através do Projecto "Saúde para Todos" que na última semana fez a entrega de alguns materiais para a reanimação neo-natal.

A pediatra portuguesa Alexandra Vasconcelos afirma que estes instrumentos vão ajudar os recém-nascidos que têm dificuldade em respirar e padecem de algum sofrimento fetal.

Equipamento

Os instrumentos vão desde insufladores a bombas de extracção de leite manual e fazem parte do lote entregue ao Ministério são tomense da saúde.

O titular da pasta, Arlindo Carvalho, salientou a importância deste apoio:

"19% das mortes de bébés recém-nascidos estão muito relacionadas com a asfixia", confirmou o Ministro, reconhecendo a necessidade de haver instrumentos que ajudem a evitar estas mortes.

A entrega destes equipamentos foi precedida de formações junto a cinco maternidades existentes no país, quatro em São Tome e uma no Príncipe.

Para Edgar Neves, coordenador do Projecto "Saúde para Todos", estas formações tiveram um papel importante porque contribuíram para a transmissão de conhecimentos aos técnicos são tomenses.

Estas informações passam por manobras tão simples como limpar as vias aéreas, fazer a estimação correcta e manobras de insuflação manual ou por compressão cardíaca.

Alexandra Vasconcelos afirma que estas técnicas ajudam o bébé a conseguir viver sem qualquer perigo de asfixia.

Esta formação de técnicos das maternidades também contou a cooperação portuguesa.

SÃO TOMÉ E PRÍNCIPE: 6 ANOS DE COOPERAÇÃO DO DEPARTAMENTO DE PEDIATRIA DO HFF

Alexandra Vasconcelos[1],Marta Ferreira[2], Helena Carreiro[3]

INTRODUÇÃO

São Tomé e Príncipe (STP), arquipélago de pequenas ilhas poderá ser um dos países mais pequenos do mundo, mas é igualmente um dos mais encantadores e desafiantes à prática clínica pediátrica.

É um país de crianças e jovens, mais precisamente 86.060 (46%) para uma população total de 187.356 habitantes de acordo com o recenseamento de 2012.[1]

A primeira ponte criada pelo departamento de Pediatria do HFF com estas crianças foi em 2008, através da realização de estágios do internato complementar de pediatria em STP e após 2010 através de missões de cooperação de curta duração e da realização de estágios de médicos São-Tomenses no departamento de Pediatria do HFF no âmbito do Projecto de Formação da Gulbenkian.



ESTÁGIOS DO INTERNATO COMPLEMENTAR DE PEDIATRIA EM SÃO TOMÉ E PRÍNCIPE

No ano de 2008, o contexto e regulamentações do internato complementar não permitiam antever que iniciativas destas fossem homologadas.

A iniciativa, persistência e acompanhamento devem-se às directoras do departamento de Pediatria e do internato médico do HFF a essa data e a concretização ao presidente do Instituto Marques de Valle-Flôr - ONGD que faz crescer a saúde em São Tomé e Príncipe.

Assim, nasceu a parceria do departamento de Pediatria do HFF com o Instituto Marquês de Valle-Flôr (IMVF), inicialmente com o planeamento, logística e estruturação de estágios opcionais de Pediatria Médica em STP e após 2010 com missões pediátricas de curta duração (1 semana) incluídas nos Projectos Saúde para Todos -Especialidades e Doenças Não Transmissíveis (DNT).

Há 26 anos que o IMVF desenvolve um projecto nacional intitulado "Projecto Saúde para Todos", que tem como principal objectivo a criação de uma rede de prestação de cuidados de saúde primários.[2] A sua metodologia de acção no terreno foi fundamental para a organização da actividade assistencial pediátrica dos estágios a nível de cuidados primários e hospitalares.

SERVIÇOS DE SAÚDE EM STP

No País, ao nível distrital, existem três escalões operacionais: os Centros de Saúde, os Postos de Saúde e os Postos de Saúde Comunitários. Existem assim, na ilha de São Tomé, um Hospital (Hospital Central Dr. Ayres de Menezes), seis Centros de Saúde Distritais, 26 Postos de Saúde e 17 Postos de Saúde Comunitária.[2]

A capacidade de intervenção na área da saúde está muito limitada pela gritante escassez de recursos humanos e materiais. Segundo a Organização Mundial de Saúde, São Tomé e Príncipe sobressai ainda pelas elevadas taxas de mortalidade infantil. Num país onde 46% de população são crianças e jovens só há duas pediatras (uma São-Tomense e uma da cooperação cubana). A restante equipa é composta por médicos que após a licenciatura foram alocados ao serviço de Pediatria ganhando experiência ao longo dos anos. Os cuidados à criança a nível distrital/cuidados primários são predominantemente assegurados por enfermeiros e as consultas por alguns dos referidos médicos hospitalares.

HOSPITAL DR. AYRES DE MENEZES (HAM)

A equipa médica é constituída por dez médicos que repartem a sua actividade pelas duas enfermarias de Pediatria (I: dos 0-24 meses; II:> 24 meses) com 80 camas, pela maternidade com 6 incubadoras onde são internados recém-nascidos de termo e pretermo, mas que, por falta constante de energia e oxigénio, servem frequentemente apenas de berço para os recém-nascidos. Há igualmente a consulta externa e serviço de urgência com um gabinete pediátrico.

Anualmente, presta assistência a mais de 20 000 crianças, das quais 4 000 em regime de internamento, sendo o número de partos superior a 1000/mês.

A ACTIVIDADE ASSISTENCIAL

O esquema do estágio consistiu na realização de consultas de Pediatria geral a nível dos cuidados primários no PMI (Protecção Materno-Infantil) no Distrito de Água Grande na cidade de São Tomé, assim como nos distritos periféricos de

[1]Assistente Hospitalar, Serviço de Pediatria, Centro Hospitalar do Oeste
[2]Assistente Hospitalar, Serviço de Pediatria, Hospital Prof. Doutor Fernando Fonseca, EPE, Amadora, Portugal
[3]Chefe de Serviço, Directora do Departamento de Pediatria, Hospital Prof. Doutor Fernando Fonseca, EPE, Amadora, Portugal

Recebido 10/12/14; Aceite 18/12/14

Guadalupe (Lobata), Lembá (Neves) e Caué (S. João dos Angolares). Prestaram assistência aos partos e apoio às maternidades do hospital e das maternidades dos centros de saúde de Lobata, Neves e Angolares. Alguns internos realizaram ainda durante uma semana actividade clínica no Hospital Manuel Quaresma da Ilha do Príncipe.

A única vantagem de se estar livre de burocracias informáticas, receituários, exames complementares e afins é que a observação das crianças a nível da consulta é muito prática, rápida e sem agendamentos. Bem cedo pela manhã os bancos dos corredores da entrada dos centros de saúde facilmente ficam cheios de mães com crianças embrulhadas nas suas capulanas que serenamente aguardam a sua vez para a consulta de pediatria.

Em média, cada interno realizou 20 a 30 observações por dia com um total de consultas de Pediatria geral (primeiras e subsequentes) entre 280 e 400.

As principais patologias foram de etiologia infecciosa (60%) nomeadamente infeções respiratórias, gastrointestinais, dermatológicas, e malária; nutricional (10%); hematológicas (10%) e seguimento (20%). Pela sua frequência e relevância salientam-se os seguintes diagnósticos clínicos: bronquiolites, asma, pneumonia, gastroenterites, parasitoses intestinais, dermatofitoses, anemias carenciais, drepanocitose e desnutrição.

A nível hospitalar os internos exerceram a sua actividade no internamento pediátrico, sala de cuidados "intensivos", consulta e urgência.

A época do ano em que os estágios foram realizados permitiu diferentes vivências profissionais. De referir que na época sazonal das chuvas sempre que necessário, era frequente o internamento de duas crianças a partilharem a mesma cama/berço. A média de crianças internadas por período de estágio oscilou entre as 80-120 por enfermaria. Durante o estágio, o interno foi, em média, responsável pela observação de 5 crianças/dia, seguindo no total a evolução clínica de cerca de 40 crianças.

Os principais grupos nosológicos das crianças internadas durante o estágio de 2008 estão apresentados no gráfico 1.

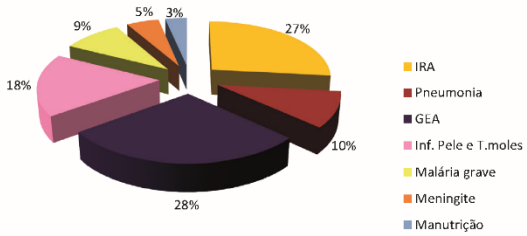


Gráfico 1 – Movimento da Enfermaria de Pediatria (Setembro e Outubro de 2008). Fonte: Centro de Estatística do Hospital Dr. Ayres de Menezes (IRA – Infecções Respiratórias Agudas)

O trabalho diário na enfermaria, urgência e maternidade permitiu abordar casos como kwashiorkor, tétano, malária cerebral e suas complicações, lactentes com obstruções intestinais devido à administração de medicamentos tradicionais, malformações congénitas entre outras.

Trabalhar num hospital sem recursos equivale a viver em angústia. A fim de dar resposta às situações há que encontrar alternativas de resolução. A indiferença pode custar a vida de uma criança.

Foi marcante a real cooperação, via e-mail, entre os internos e o departamento de Pediatria do HFF na discussão de vários casos complicados. No terreno, alguns internos puderam ainda contar com a visita da direção do serviço, que partilhou as experiências intensas e inesquecíveis, enfrentando a escassez de recursos e a dificuldade do tratamento e diagnóstico das crianças seguidas e até as etapas de pedidos e burocracias que envolvem a evacuação de crianças para Portugal.

A nossa Pediatria aterrou em São Tomé e Príncipe numa era pré-Telemedicina, pré-Projecto Especialidades, pré-Projecto Doenças Não Transmissiveis o que nos trouxe o benefício de testemunhar o quanto foi possível construir e investir na saúde deste país em tão poucos anos.

Experiência que constituiu um desafio pessoal e profissional riquíssimo para quem teve a oportunidade de a concretizar. Em STP as famosas guidelines caem por terra e o exercício da Pediatria e sua arte de cura passam a contar apenas com o estetoscópio, otoscópio, espátula e semiologia clínica.

Decorridos seis anos, 5 internos de Pediatria do HFF (Alexandra Vasconcelos 2008, Marta Ferreira 2009, Joana Martins 2011, Andreia Martins e Susana Pacheco 2013), entre outros de diversas unidades hospitalares do país, exerceram por estágio, 3 meses de trabalho no terreno.

PARA ALÉM DAS ESTATÍSTICAS...

A importância de conceitos tão esquecidos ou menosprezados para a prática clínica europeia como a escassez de recursos, o valor da saúde ambiental, o acesso a água potável e saneamento, a influência da cultura, crenças e o uso das curas alternativas e afins são condicionantes muito poderosas nestes palcos de vida.

Em 2008 a mortalidade infantil em STP era de 48%0 e nas crianças abaixo dos 5 anos de 60%0 comparativamente com os dados em Portugal de 3 e 4%0 respectivamente.[3]

A elevada mortalidade infantil em STP está relacionada com as seguintes causas: neonatal (32%), pneumonia (21,2%), diarreia (16%), sarampo (4,8%), VIH (3,7%), malária (0,6%), e outras (18%).[3] (Fig. 1)



PROPOSTA DA PEDIATRIA PARA STP



Acreditámos que era possível contribuir um pouco mais e aderir ao 4º Objectivo para o Desenvolvimento do Milénio (ODM) da OMS, com o ideal de diminuir a mortalidade infantil nomeadamente neonatal.

Foi então agarrado o desafio de fortalecer a prática da pediatria neste país em relação a áreas vulneráveis como a neonatologia, pneumologia e infecciologia.

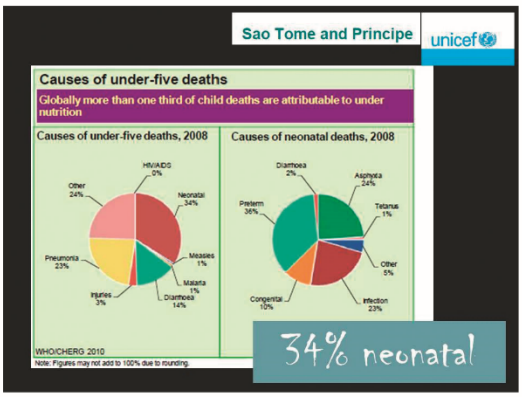


Figura 1 – Causas da mortalidade em crianças <5 anos e causas de mortalidade neonatal em 2008 em São Tomé e Príncipe. Fonte: Unicef

Verificamos que a área do apoio ao recém-nascido (RN) se encontrava muito precária, com a inexistência de material simples auxiliar à adaptação do RN à vida extra-uterina assim como o desconhecimento do algoritmo de actuação de reanimação neonatal preconizado pela OMS para os países em vias de desenvolvimento.

Reconhecendo que muitos dos óbitos neonatais que ocorrem neste países seriam evitáveis ao proporcionar melhor qualidade na vigilância pré-natal, parto e assistência neonatal, principalmente na sala de partos e sabendo que a assistência ao parto em STP é realizada por pessoal de saúde em 81% dos casos (45% dos casos por uma enfermeira, 25% por uma parteira auxiliar, 9% por um médico e 21% por outro/nenhum), investir na capacitação e formação dos mesmos permitiria antever uma melhoria deste indicador de saúde.[2] O IMVF acolheu de braços abertos o nosso projecto.

O ano de 2009 permitiu a fase de preparação em Portugal com o desenho e construção dos placares, criação do material didático, burocracias e afins. O regresso a STP para a implementação no terreno teve início em Maio de 2010 com uma missão de longa duração de Alexandra Vasconcelos.

A missão visou os seguintes pontos estratégicos para a área da neonatologia na formação dos profissionais de saúde infantil:

1) Reforço da competência dos quadros técnicos com acções de formação. Dois formadores (Helena Carreiro e Alexandra Vasconcelos) realizaram 8 cursos permitindo a formação de 110 profissionais de saúde (95% parteiras) (Tabela I). As acções de formação respeitaram as recomendações da OMS para a reanimação neonatal para países com recursos limitados. As técnicas foram demonstradas através de vídeos exemplificativos e com treino prático individual em manequins. Foi distribuído dossier com a explicação teórica. Em relação ao apoio assistencial ao recém-nascido (RN), foi feito o ensino da identificação e tratamento do RN com risco infeccioso, icterícia, conjuntivite e a abordagem ao RN filho de mãe com VIH, tuberculose ou sífilis.
2) Colocação de placares em lona com o algoritmo da reanimação neonatal nas salas de parto de todas as maternidades do país. O algoritmo foi concebido principalmente através de desenhos que permitissem um fácil seguimento e visualização do procedimento.
3) Distribuição de equipamento básico para a reanimação neonatal nas sete maternidades do país.
4) Informação veiculda aos pais sobre o reconhecimento dos sinais de alarme do RN através da impressão no Boletim de Saúde Infantil de uma tabela com desenhos ilustrativos dos mesmos. (Fig. 2)
5) Garantia da sustentabilidade e continuidade do programa com a co-responsabilidade da enfermeira chefe de cada unidade de saúde em relembrar o algoritmo de actuação da reanimação neonatal e pela repetição do curso anualmente por parte da equipa pediátrica portuguesa.



Tabela 1 – Programa das formações teórico-práticas para as enfermeiras parteiras do País.

As acções de formação sobre a abordagem e actuação peri-parto e pós-parto, como as referidas, contribuem para uma redução da mortalidade neonatal entre 6 a 42%.[4-7] Estratégias de cooperação desta natureza contribuem igualmente para o desenvolvimento sustentado de um país com recursos limitados como STP, accionando mudanças reais nas condutas individuais dos profissionais de saúde, indo de encontro ao 4º ODM.

Este projecto foi galardoado com o 1º Prémio da área das subespecialidades no Congresso de Pediatria Médica Hospital Dona Estefânia em Julho de 2011.

A PEDIATRIA E AS MISSÕES DE CURTA DURAÇÃO

No âmbito do projecto das Doenças Não Transmissíveis (DNT) a Pediatria focou a sua intervenção nas seguintes áreas:

1) Prevenção de doenças não transmissíveis (Helena Carreiro, Marta Ferreira, Alexandra Vasconcelos): em junho de 2011 foi realizada a primeira formação de formadores (20 formandos) nas áreas de suporte básico de vida neonatal e pediátrico, traumatismos, queimaduras e intoxicações. Para este efeito foi adquirido e doado um manequim de simulação pediátrico de forma a dar continuidade e estender a formação a todos os profissionais de saúde.
2) Saúde Sexual na Adolescência (Helena Carreiro, Marta Ferreira): em Novembro de 2011 em articulação com o programa de rastreio do canco do colo do útero, foi criado um projecto de saúde sexual e prevenção de infecções sexualmente transmissíveis (IST) na adolescência através da formação de profissionais de saúde e de professores do liceu em paralelo com campanhas de divulgação nos orgãos de comunicação social. Em STP para além do problema da gravidez na adolescência é também pertinente o reforço continuado para a adopção de práticas sexuais seguras atendendo aos bons indicadores que o país apresenta na prevenção da epidemia do VIH/Sida.
3) Doença Respiratória e Asma (Helena Carreiro, Alexandra Vasconcelos, Marta Ferreira): em Junho de 2012, em articulação com a equipa de pneumologia do Hospital Pulido Valente, foi elaborado um projecto de ensino dos profissionais de saúde na abordagem, diagnóstico e tratamento das doenças respiratórias com principal ênfase na asma. A elevada prevalência da patologia respiratória neste país associada a várias limitações (inexistência de aparelhos de ventilação invasiva ou não-invasiva, de câmaras expansoras, assim como a escassez de aparelhos de oxigenoterapia suplementar e de métodos de diagnóstico) tem repercussões significativas na qualidade de vida, morbilidade e mortalidade infantil sendo por isso essencial a optimização das etapas da prevenção e correcto tratamento dos episódios agudos. Foi também feito o ensino e entrega de câmaras expansoras tanto na urgência hospitalar como nos principais centros de saúde atendendo à melhor eficácia deste dispositivo médico face à sua independência da eletricidade comparativamente com os aparelhos de nebulização.
4) Doenças da Infância (Helena Carreiro, Marta Ferreira, Susana Pacheco): em Novembro de 2013, foram realizadas acções de formação destinadas aos profissionais de saúde que visaram o reforço das estratégias de diagnóstico, tratamento e seguimento das patologias infecciosas mais frequentes da infância.

ENSINO PARA A SAÚDE

O recurso a esta viabilidade é imprescindível atendendo à realidade do país. Veicular informação médica básica à população é uma arma excelente que pode proporcionar a construção de uma mente colectiva educada e alerta para as questões pertinentes no combate da redução da mortalidade infantil.

Como anteriormente referido todas as missões utilizaram diversas estratégias de divulgação de conteúdos relevantes para a diminuição da mortalidade e para uma optimização da prática clínica pediátrica no país destinados tanto à população em geral como específica para os profissionais de saúde usando os orgãos de comunicação social bem como cartazes e folhetos de informação:

1) Mortalidade neonatal: capacitação da população na identificação dos sinais de alarme no recém-nascido. Aproximadamente 40% da mortalidade infantil ocorre no primeiro mês de vida e a precariedade do conhecimento das mães em STP na identificação dos sinais de alarme e cuidados básicos ao recém-nascido conduziu-nos à proposta para a implementação de uma acção conjunta com o Ministério da Saúde de STP, elaborando uma tabela com os desenhos dos sinais de alarme do RN que permitissem uma rápida detecção e interpretação por parte das mães.[4-7] Autocolante colado no boletim da criança entregue aos pais na altura do nascimento e também impresso no formato de cartaz que foi distribuído pelos vários postos de saúde e centros de saúde. (Fig. 2)

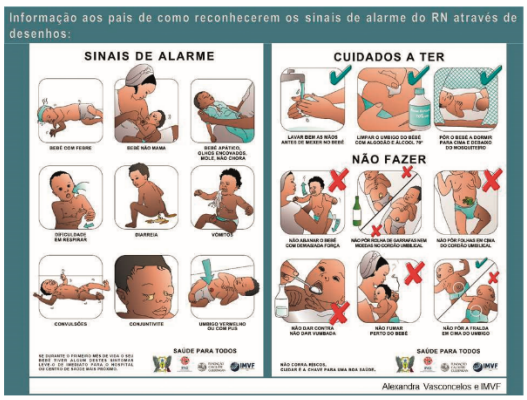


Figura 2 – Autocolante para o Boletim de Saúde Infantil alertanto para os sinais de alarme dos recém-nascidos

2) A capacitação dos profissionais de saúde sobre a reanimação neonatal e o apetrechamento das maternidades do país com o equipamento básico para a sua execução foi alvo de notícia difundida através do Repórter África do canal RTP África assim como pelo Telejornal da TVS (televisão são-tomense).
3) Saúde sexual na adolescência - foram realizadas várias acções de comunicação através da TVS, rádios locais, algumas multidisciplinares em conjunto com colegas da ginecologia também em missão de cooperação e com professores do liceu nacional.
4) Folhetos informativos destinados aos profissionais de saúde com ensino e estratégias simples de acção adaptadas aos países em vias de desenvolvimento: dor na criança (doses pediátricas e frequência de administração dos diferentes analgésicos) (Fig. 3) e queimaduras na infância - acidente frequente nas crianças São-tomenses atendendo aos fogareiros no exterior das habitações e precárias medidas de segurança nessas áreas (actuação correcta e seu tratamento). (Fig. 4)



Figura 3 – Folheto informativo destinado aos profissionais de saúde para a abordagem da dor na criança

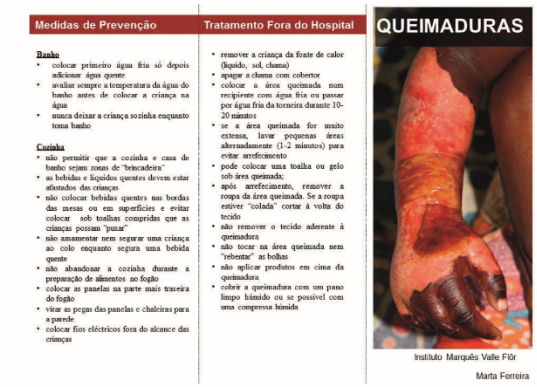


Figura 4 – Folheto informativo destinado aos profissionais de saúde para a abordagem das queimaduras na criança

OUTRAS ACÇÕES

Em Portugal a relação com São Tomé e Príncipe mantem-se tanto através de frequentes consultas de Telemedicina assim como através do intercâmbio proporcionado pela Fundação Calouste Gulbenkian, com o intuito de dar a conhecer aos médicos São-Tomenses outra realidade e práticas clínicas do mundo pediátrico.

As missões de curta duração terão sempre que apostar na formação contínua e adequada à realidade de STP dos colegas que exercem as suas actividades na área da Pediatria. A continuidade de uma estratégia de comunicação e intercâmbio de informação via e-mail ou pela Telemedicina, é uma ferramenta preciosa e extremamente eficaz de cooperação entre o serviço de Pediatria de São Tomé e Portugal contribuindo para um enriquecimento bilateral ímpar.

O NOSSO ENRIQUECIMENTO

É unânime a sensação que todos partilhamos que São Tomé e Príncipe, suas crianças, mundividências, saúde e doença nos enriqueceram muito mais do que qualquer acção, cooperação ou ponte que tenhamos tentado lançar para esse espaço encantado e encantador, contudo ainda tão frágil e aquém de perfeito. São Tomé e Príncipe criou em nós um laço para a vida e a vontade catalisadora de contibuir para um mundo melhor.

Um agradecimento especial à equipa no terreno do IMVF e votos que mantenham a energia contagiante, quotidiana e inesgotável em proporcionar "Saúde para Todos" em São Tomé e Príncipe.

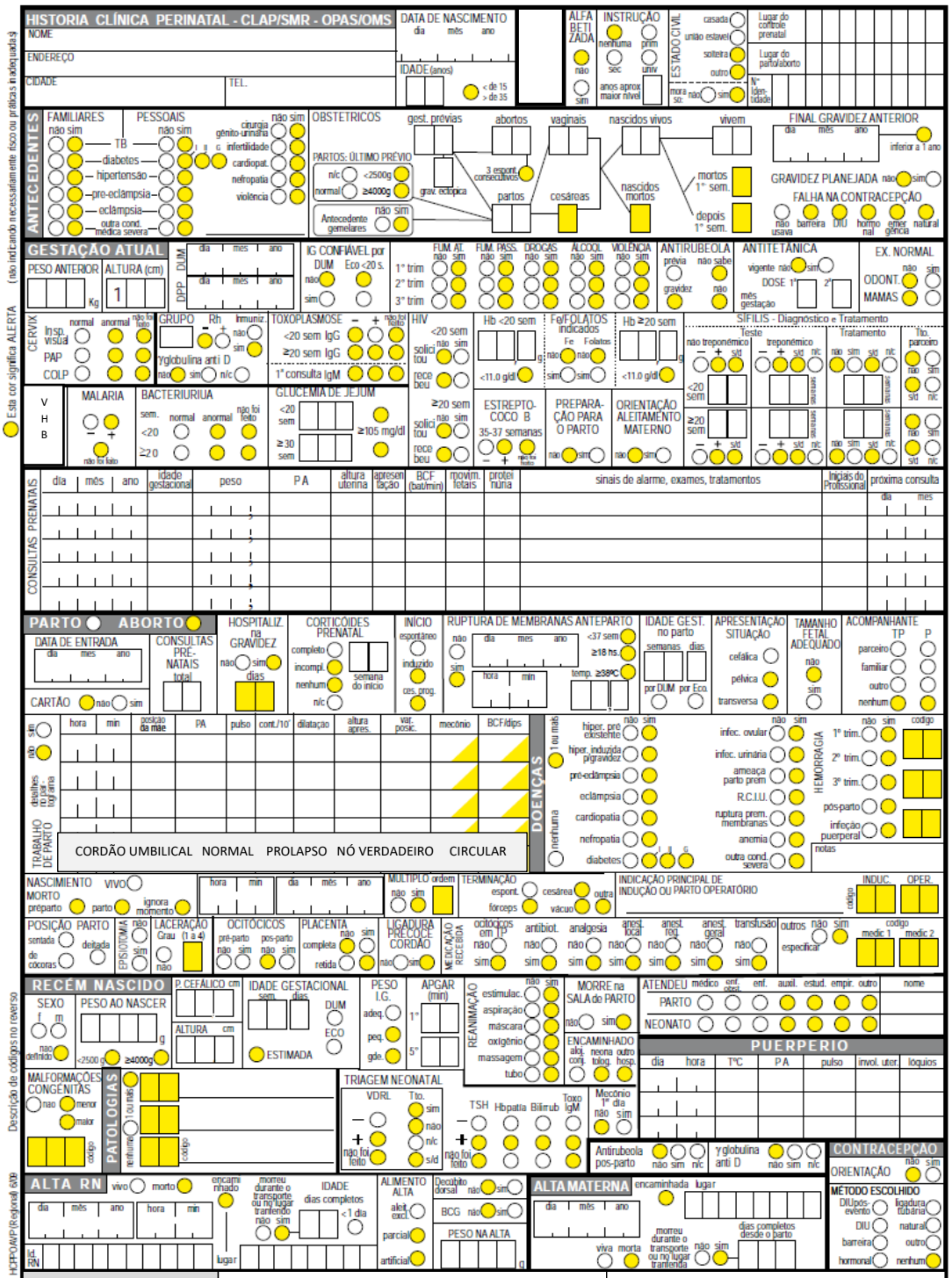


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APPENDIX 8 | Questionnaire and Variables_ definition and operationalization

Centro Latino-Americano de Perinatologia da Saúde da Mulher e Reprodutiva (CLAP/SMR) da Organização Pan-Americana da saúde/Organização Mundial da Saúde (OPAS/OMS).



Identificação: □□□□.□□□□.□□.□□

Nº de entrada: _____

IDENTIFICAÇÃO	
Número	
Nome de casa	
Residência habitual	
Número telemóvel	

VIGILÂNCIA PRÉ-NATAL	
Onde foi vista?	
De quantos meses estava na 1ª consulta?	|__| meses
Quantas consultas teve no total?	|__|__| vezes
Tomou algum medicamento durante a gravidez?	1. Sim 2. Não 3. Não sabe
Qual?	
Para quê, sabe?	
Tomou medicamento tradicional durante a gravidez	1. Sim 2. Não 3. Não sabe
Tomou medicamento tradicional /chá para provocar o parto?	1. Sim 2. Não 3. Não sabe

CONHECIMENTO DOS SINAIS DE ALARME DO RN	
Convulsões/espasmos/rigidez	1. Sim 2. Não 3. Não sabe
Dificuldade/respiração rápida	1. Sim 2. Não 3. Não sabe
Bebé muito leve (peso < 2.5 kg)	1. Sim 2. Não 3. Não sabe
Letargia/inconsciente	1. Sim 2. Não 3. Não sabe
Febre, i.e, o corpo com uma tempertura muito elevada	1. Sim 2. Não 3. Não sabe

CARACTERÍSTICAS SÓCIO-DEMOGRÁFICAS	
Casa	1. Madeira 2. Cimento
Número de quartos	1. Um 2. Dois 3. Três 4. Mais de três
Quantos adultos lá vivem	
Quantas crianças	
Fonte da água que bebe	1. Água canalizada 2. Água engarrafada 3. Poço 5. Água fontanário 6. Rio 7. Água da chuva
Tipo de instalação sanitária	1. Casa-de-banho privada 2. casa-de-banho pública 3. Latrina contruída cimento 4. Latrina nos arbustos
Fonte de luz em casa?	1. Eletricidade 2. Kerosene 3. Gás 4. Energia solar
Fonte para cozinhar?	1. Madeira 2. Carvão 3. Electricidade

PAI	
Que idade tem o pai da criança?	Idade (anos) |__|__| 1 = <20 anos 2 = 20-29 anos 3 = 30-39 anos 4 = 40-49 anos 5 = >49 anos
Ele acompanhou a gravidez?	1. Sim 2. Não
O pai do seu bebé frequentou a escola?	1. Sim 2. Não 3. Não sabe
Qual é o grau de ensino mais elevado dele?	1 = Nenhum 2 = Primário 3 = Secondário 4 = Universitário
Com que frequência ele bebe cacharamba ou álcool?	1 = todos os dias 2 = só ao domingo 3 = em festas 4 = não bebe 5= não sabe/não responde

QuickTapSurvey

QUESTIONÁRIO_FASE 1

Código do Consentimento Informado_____

Data do questionário:

IDENTIFICAÇÃO

Nome Mãe

Data nascimento Mãe

Idade da Mãe quando engravidou pela 1ª vez:
Presente gravidez na adolescência (15 a 19 anos): 0 =não, 1=sim

Grupo sanguíneo
- Testou (0=não, 1=sim)
- Qual grupo (0=A, 1=B, 2=0)
- Grupo Rh (0= negativo, 1 =positivo)

Residência

Distrito

VIGILÂNCIA PRÉ-NATAL

Centro de Saúde_

Índice Obstétrico
- número de gravidezes -
- número de partos -
- número de abortos -
- número de filhos nado-vivos -

Número de cesarianas anteriores
Filhos mortos (0=não, 1=sim)
- Nado-morto
- Na 1ª semana de vida
- No 1º mês de vida:
- Após 1º mês de vida:

Fim da gravidez prévia (0= mais de 2 anos, 1=há menos de 2 anos)
A.R.O Alto Risco Obstétrico (0=não, 1=sim)

Motivo

0=Parto anterior com cesariana
1=Parto anterior com forceps ou ventosa
2=Parto anterior com complicação hemorrágica
3=Primigesta adolescente < 15 anos
4=Grávida >35 anos
5=Teve 6 ou + partos
6=Parto anterior com nado morto ou RN óbito 1ª semana
7=Parto prolongado
8=outro

Antecedentes Familiares relevantes (0=não, 1=sim, 2=não sabe)

Se sim, quais:

Antecedentes da Mãe relevantes pré-gravidez (0=não, 1=sim)

Se sim, quais:

0=Diabetes
1=HTA
2=Infeção Urinária
3=Dça cardíaca
4=Dça alérgica
5=Tromboflebites
6=Sífilis
7=Células Falciformes
8=Incompatibilidade

Outra: (a preencher livre)_____

Contraceção (0=não usava, 1=preservativo, 2=DIU, 3=pílula, 4=natural)

16. Falha na contraceção (0=não, 1=sim)

GESTAÇÃO ATUAL

64. Data da Última Menstruação (DUM)
65. Data Prevista para o Parto (DPP)
~~66~~
1ª Consulta da gestação atual (semanas de gravidez: 1 a 41 semanas)
Total consultas (0 a 12)
Gravidez mal vigiada (0=não, 1=sim)

Ecografia fetal (0=não fez, 1=sim fez)

IG confiável por ECO Fetal < 20 sem (0=não, 1=sim)

Quantas Ecos Fetais fez (0=não fez, 1=uma eco, 2= duas, 3=três e 4=quatro)

Alguma alteração? Se sim qual:

Fansidar (0=não fez, 1=1 dose, 2=2 doses)

Mosquiteiro impregnado (0=não entregue, 1=sim entregue)

Ácido Fólico/Ferro

Vacina antitetânica (0=zero doses, 1=1, 2=2, 3=3, 4=4, 5=5 completa)

Teste VDRL Sífilis (0=não testou, 1=um teste, 2= dois testes)

Resultados positivos (0=não, 1=sim)

Fez penicilina (0=não, 1=sim)

Parceiro (0=não testado, 1= testado e atb, 2= testado e não fez atb, 3= não testado mas fez atb)

Teste VIH (0=não testou, 1=um teste, 2= dois testes)

Resultados positivos (0=não, 1=sim)

Vacina VHB (0=não testou, 1=um teste, 2= dois testes)

Resultados positivos (0=não, 1=sim)

RN fez vacina VHB nas primeiras 48h vida (0=não, 1=sim)

Hemoglobina IG < 20 semanas (0=Não fez, 1= Hg <11 g/dL e 2=>11 g/dL)

Resultado:

Hemoglobina IG > 20 semanas (0=Não fez, 1= Hg <11 g/dL e 2=>11 g/dL)

Resultado:

Glicémia IG < 20 semanas (0=Não fez, 1= Glicémia <105 mg/dL e 2=>105 mg/dL)

Resultado:

Glicémia IG > 20 semanas (0=Não fez, 1= Glicémia <105 mg/dL e 2=>105 mg/dL)

Resultado:

Teste Malária (0=não testou, 1=um teste, 2= dois testes)

Resultados positivos (0=não, 1=sim)

Teste Bacteriúria (0=não testou, 1=um teste, 2= dois testes)

Teste Bacteriúria 1 Resultados positivos (0=não, 1=sim)

Se sim, qual o resultado: 0=só leucócitos, 1=só piócitos, 2=leucócitos e piócitos

Fez antibiótico (0=não, 1=sim)

se sim, qual antibiótico (0= amoxicilina, 1= ampicilina, 2=outro)

se outro, qual _____

nota_____

Teste Bacteriúria 2 Resultados positivos (0=não, 1=sim)
Qual o resultado: 0=só leucócitos, 1=só piócitos, 2=leucócitos e piócitos
Fez antibiótico (0=não, 1=sim)
se sim, qual antibiótico (0= amoxicilina, 1= ampicilina, 2=outro)
se outro, qual _____
nota_____

Teste Fezes (0=não testou, 1=um teste, 2= dois testes)
Resultado 1º teste (0=negativo, 1=positivo)

Qual o agente identificado
Fez tratamento (0=não, 1=sim)
se sim, qual (0= albendazol, 1= mebendazol e 2=……)
Resultado 2º teste (0=negativo, 1=positivo)
(192) Qual o agente identificado
Fez tratamento (0=não, 1=sim)
se sim, qual (0= 1= e 2=)
Nota_____

Teste exsudado vaginal (0=não testou, 1=um teste, 2= dois testes)
Resultados positivos (0=não, 1=sim)
Teste 1 positivo - Qual o agente identificado: (opção de identificar mais do que 1 opção)
1= candida, 2=bacilos gram (+), 3=bacilos gram (-), 4=cocos gram (+), 5=cocos gram (-), 6=muitos leucócitos)
Fez tratamento (0=não, 1=sim)
se sim, qual (0= nistatina óvulos 1=clotrimazol, 2=nistatina + clotrimazol, 3=amoxicilina, 4=outro)
Teste 2 positivo - Qual o agente identificado: (opção de identificar mais do que 1 opção)
1= candida, 2=bacilos gram (+), 3=bacilos gram (-), 4=cocos gram (+), 5=cocos gram (-), 6=muitos leucócitos)
Fez tratamento (0=não, 1=sim)
se sim, qual (0= nistatina óvulos 1=clotrimazol, 2=nistatina + clotrimazol, 3=amoxicilina, 4=outro)

Pesquisa Células Falciformes (0=não, 1=sim)
Resultado do teste: positivo ou negativo
Se positivo qual a percentagem?_____

WIDAL (0=não fez, 1=fez)
(0=negativo, 1=positivo)
Título:

Patologia materna durante a gravidez (0=não, 1=sim)
Quais (opção de escolher mais do que uma opção)
Anemia

Parasitose intestinal
Infeção Urinária
Infeção Vaginal
Candidiase
HTA
Pré-eclampsia
Eclampsia
Diabetes gestacional
Células Falciformes
Tuberculose
Hepatite
Outra

Espaço livre para especificar a outra dça_____

PARTO

Maternidade: 0=não, 1=sim
Se não onde: casa, outra maternidade, a caminho

Grávida transferida 0=não, 1=sim
Se transferida de onde/quando_____
Motivo_____

Parto: 0=eutócico 1=distócico

Parto (0=espontâneo, 1=induzido, 2=cesariana programada, 3=cesariana de urgência)

Tipo de parto distócico (1=ventosa, 2= fórceps, 3=cesariana)
Indicação do parto distócico_ (espaço em aberto para resposta livre)_____

Quem realizou o parto (0=em casa, 1=parteira, 2=obstetra, 3=outro)

Apresentação (0=cefálica, 1=pélvica, 2=transversa)
Pródromo 0=não, 1=sim

Rutura de membranas ante parto (0=não, 1=sim)

Gravidez gemelar (0=não, 1=sim)
Episiotomia (0=não, 1=sim)
Laceração (0=não, 1=grau 1, 2=grau 2, 3=grau 3 e 4=grau 4)
Medicação à Mãe pré-parto
Antibioticoterapia (0=não, 1=sim)
Analgesia (0=não, 1=sim)
Anestesia geral (0=não, 1=sim)
Anestesia regional (0=não, 1=sim)

Transfusão (0=não, 1=sim)

Alteração no cordão umbilical (0=não, 1=prolapso, 2=nó verdadeiro, 3=circular)
Líquido amniótico claro LAC (0=não, 1=sim)
Hemorragia materna (0=não, 1=1ºT, 2=2ºT, 3=3ºT, 4=pós-parto)
Infeção puerperal (0=não, 1=sim)

Alta materna (0=saudável, 1= doença pós-parto, 2= morte materna)
Se doença qual_____

RECÉM-NASCIDO

Identidade do RN_____

RN: CASO ou CONTROLO

Nado-Morto (0=não, 1=sim)

Data nascimento
Hora (incluir opção de pôr os minutos)
Qual a Idade gestacional IG
Sexo
Peso ao nascer
Peso ao nascer de alerta (0=<2500g, 1=>4000g)
Perímetro cefálico
Comprimento

APGAR 1º minuto
APGAR 5º minuto
APGAR 10º minuto
REANIMAÇÃO NEONATAL (0=não, 1=ligeira, 2=completa)
Morte na sala de parto (0=não, 1=sim)
Destino (0=com a mãe, 1=com a mãe mas com doença/suspeita, 2= internado na sala incubadoras)
Mecónio no 1º dia (0=não, 1=sim)
Aleitamento (0=materno exclusivo bom, 1=materno exclusivo fraco, 2=parcial e 3=artificial)

Prematuridade (0=não, 1=sim)
Asfixia perinatal (0=não, 1=sim)
Risco Infecioso (0=não, 1=sim)
RN com febre (0=não, 1=sim)
RCIU (0=não, 1=sim)
Se sim: simétrica ou assimétrica
Microcefalia (0=não, 1=sim)
RN suspeita Sépsis (0=não, 1=sim)
RN com suspeita de Células Falciformes (0=não, 1=sim)
Malformações congénitas (0=não, 1=sim mas minor, 2= sim e major)

Quais?

Outras patologias do RN na maternidade (0=não, 1=sim)
Quais?
Fez tratamento? (0=não, 1=sim)
Com o quê?

Se morte com quantas horas de vida
Se morte com quantos dias de vida
Alta da maternidade com quantos dias de vida
Saudável à alta (0=não, 1=sim)
DATA DA ALTA DO RN DA MATERNIDADE
Fez colheita de sangue para estudo (0=não, 1=sim)
Resultado do exame FCML____

ESPAÇO ABERTO PARA OUTRAS NOTAS……

ENTREVISTA À MÃE

Telemóvel (telemóvel 1 _____ telemóvel 2_____) pôr um campo livre para referir o nome ou qual o familiar

Profissão: mudar as opções para estarem de acordo com o INE-STP
Profissional não qualificado
Operário, maquinista e equip. pesados
Artesãos e trabalhadores qualificados
Atividade de serviço e comércio
Atividade administrativa
Profissão Intermediária
Profissão Intelectual e Científica
Executivo, legislativo e Quadro superior
Acrescentar espaço livre para especificar profissão_____

Escolaridade (0=nenhuma, 1=primário incompleto, 2=primário completo, 3=secundário incompleto, 4= secundário completo, 3=universitário incompleto, 4=licenciatura)

Com quem vive: 0= ela e marido, 1= ela e homem, 2=ela sozinha, 3=ela e mãe dela, 4= ela e outros familiares
Quantas crianças cuida nessa casa:
Quantos adultos

Tipo de Casa (madeira, cimento, sanzala, mista)
Número quartos

Fonte de água que bebe (0=canalizada, 1=engarrafada, 2=chafariz, 3=tanque, 4=poço, 5=rio, 6=quintal, 7=quintal vizinha, 8=quintal estado)

Tipo instalação sanitárias (0=casa-de-banho, 1=latrina, 2=mato, 3=praia)
Fonte de luz em casa (0=energia, 1=petróleo, 2=vela)
Fonte para cozinhar (0=lenha, 1=petróleo, 2=carvão, 4=gás, 5=fogão da china)

Vive sozinha (0=não, 1=sim)

PAI

Idade (0=NS, 1=<20 anos, 2=20-29, 3=30-39, 4=40-49, 5=>49 anos)
Escolaridade (0=nenhuma, 1=primário incompleto, 2=primário completo, 3=secundário incompleto, 4= secundário completo, 5=universitário, 6=não sabe)

Profissão: mudar as opções para estarem de acordo com o INE-STP

- Profissional não qualificado
- Operário, maquinista e equip. pesados
- Artesãos e trabalhadores qualificados
- Atividade de serviço e comércio
- Atividade administrativa
- Profissão Intermediária
- Profissão Intelectual e Científica
- Executivo, legislativo e Quadro superior

Acrescentar espaço livre para especificar profissão_____

Escolaridade (0=nenhuma, 1=primário incompleto, 2=primário completo, 3=secundário incompleto, 4= secundário completo, 3=universitário incompleto, 4=licenciatura)

Consanguinidade (0=não, 1=sim, 2= NS)
Há quanto tempo estão juntos (<1 ano, 1-2 anos, 3-4, 4-5, 6-7, 7-8, >8 anos)
Pai tem quantos outros filhos só dele:
Quantas mulheres/casas tem (0=NS, 1=1, 2=2, 3=3, 4=>4)
Bebidas alcoólicas (0=não significativa, 2=consumo habitual, 3=consumo em demasia)
Acompanhou a gravidez (0=não, 1=sim)

Altura Mãe (0=não sabe, 1= <150, 2= >150 cm)
Contraceção (0=não usava, 1=preservativo, 2=DIU, 3=pílula, 4=natural)
Gravidez planeada (0=não, 1=sim, 2=não sabe/não responde, 3=não perguntado)
Teve aborto antes (0=não, 1=sim)
    Se sim: involuntário ou provocado
Hábitos de risco durante a gravidez (0=não, 1=sim)
    Se sim, qual
Bebidas alcoólicas (0=não significativa, 2=consumo habitual, 3=consumo em demasia)
Tomou Fansidar (0=não, 1=sim)
Tomou ácido fólico e sal ferroso (0=não, 1=sim)
Tomou medicamentos tradicionais (0=não, 1=sim)

Qual/quais

Quer fazer planeamento familiar pós-parto (0=não, 1=sim, 2=não sabe)

Conhecimento dos sinais de alarme do rn (0=não, 1=sim)

RESULTADO teste HEXAGON

(0=negativo, 1=positivo, 2=não realizado)

ESPAÇO ABERTO PARA OUTRAS NOTAS……

QUESTIONÁRIO_1º FOLLOW-UP

FOLLOW-UP DO RECÉM-NASCIDO NO 1º MÊS DE VIDA

Código do Consentimento Informado_____

Follow-up RN inicialmente: caso ou controlo

Entrevista: telefone ou observação em consulta

RN follow-up >1º mês de vida: continua controlo ou passou a caso

QUESTIONNAIRE

The questionnaire used in this research and data varaibles were adapted from:

i. Lewycka SO. Reducing maternal and neonatal deaths in rural Malawi : Evaluating the impact of a community- based women ' s group intervention. 2010;(October):1 of 336.

ii. Magoma MTM. The effectiveness of antenatal birth plans in increasing skilled care at delivery and after delivery in rural Tanzania a cluster randomised trial. Dr thesis, London Sch Hyg Trop Med. 2010.

1. IDENTIFICATION

No	QUESTION	CODING CATEGORIES	CODES	VARIABLE
Q1.1	Number assigned			NUMBER
Q1.2	Name of Health Unit			HEALTHUNIT
Q1.3	Interviewer´s name/ official			INTNAME
Q1.4	House Name			INTHOMENAME
Q1.5	Date of interview			DATE
Q1.6	Where do you usually live			VILLAGE
Q1.7	In what month and year were you born?			DOBPARTICIPANT
Q1.8	How old are you in complete years?			AGE

2. SOIO-DEMOGRAPHIC CHARACTERISTICS

Now I would like to ask some questions on your personal and household issues

No	QUESTION	CODING CATEGORIES	CODES	VARIABLE
Q2.1	What of the following best describes your relation with the baby´s father?	1 = Married 2 = Boyfriend 3 = Fiancé 4 = Casual acquaintance 5 = Cohabiting 6 = Divorced/separated 7 = Widowed 8 = Other (specify)		MARITALSTAT
Q2.2	How old is your partner/husband?	Age (years) |__|__| 1 = <20 years 2 = 20-29 years 3 = 30-39 years 4 = 40-49 years 5 = >49 years		AGEPARTNER
Q2.3	Is he assisting you in this pregnancy?	1. Yes 2. No		ASSIST

Q2.4	Which of the following best describes your living arrangements with this man?	1 = Live together all of the time 2 = Live together but occasionally apart for work 3 = Live apart but frequent cohabitation (return visits) 4 = Live apart, infrequent cohabitation 5 = Never live together		LIVEMOST
Q2.5	What of the following best describes your relationship?	1.Monogamous relationship 2. Polygamous relationship		RELATIONS
Q2.6	Have you ever attended school?	1. Yes 2. No		EVERSCHOOL
Q2.7	What´s the highest level of education you have: primary, secondary or higher?	1 = None 2 = Primary 3 = Secondary 4 = University		EDUCATION
Q2.8	Did your male partner or husband ever attend school?	1. Yes 2. No		PARTNER SCHOOL
Q2.9	What´s his highest level of education: primary, secondary or higher?	1 = None 2 = Primary 3 = Secondary 4 = University		
Q2.10	What is your occupation; that is, what kind of work do you mainly do?	1 = Farming 2 = Fishing 2 = Casual worker 3 = Salaried worker 4 = Small business/artisan 5 = Student 6 = No work 7 = Other (specify _____-_)		OCCUPINT
Q2.11	What´s your husband´s (partner´s) occupation?	1 = Farming 2 = Fishing 2 = Casual worker 3 = Salaried worker 4 = Small business/artisan 5 = Student 6 = No work 7 = Other (specify _____-_)		OCCUPARTNER
What of the following best describes the house you live in?				
Q2.12	House	1. Wood 2. Cement		HOUSE
Q2.13	How many rooms/divisions?	1. One 2. Two 3. Three 4.mora than three		ROOMS
Q2.14	How many adults live in the home?			ADULTS
Q2.15	How many children live in the home?			CHILDREN
Q2.16	Source of drinking water	1. In-house piped water 2. Piped water in a public tap 3. Well in residence 4. Public well 5. Spring for drinking water 6. River, canal or surface water for drinking 7. Uses rain water for drinking		WATER
	Type of toilet	1. Private flush toilet 2. Public flush toilet		TOILET

		3. Pit latrine for toilet 4. Has bush or field as latrine		
	What is the source of power for household lighting?	1. Eletricity 2. Kerosene 3. Gas 4. Solar power		LIGHT
	What is the source of power for household cooking?	1. Wood 2. Charcoal 3. Electricity		COOK
Now let us talk on some possession in your household				
Q	Do you have a mobile phone?	1. Yes 2. No		MOBILE
Q	Does your house family own a motocicle?	1. Yes 2. No		MOTO
Q	Do you own a television?	1. Yes 2. No		TV
Q	Do you have enough food for your family throughout the year?	1. Yes 2. No		FOOD
Q	How often in a year do you usually have problems in satisfying the food needs of your household?	1. Never 2. Seldom 3. Sometimes 4. Often 5. Always		FOODSATISFY
Q				
Q				

3. OBSTETRICS HISTORY Now let us talk about previous pregnancy history if you had ever had any

No	QUESTION	CODING CATEGORIES	CODES	VARIABLE
	How many pregnancies have you ever had in your lifetime including this one?			GRAVIDITY
	Have you ever had any pregnancy that was miscarried?	1. Yes 2. No 3. NA (1st pregnancy)		PREGLOSS
	How many of such pregnancies have you ever lost?			PREGLOSSNO
	How many of these were before five months? (20 weeks)			ABORTION
	How many of these were five months or beyond?			MISCARRIAGE
Thank you for the discussion so far. Let us talk on the children you ever delivered in your life				
	How many children have you ever delivered in your lifetime?			PARITY
	One of this have ever happen?	1. Live baby but died within one month of delivery 2. Live baby but died beyond one month 3. Stillbirth 4. Not applicable (had never delivered)		NEWBORNDEATH
	How many of these were born alive? (any sign of life)			BORN-ALIVE
	How many children you had ever delivered are alive today?			CHILD-ALIVE
	How many died?			ALIVE-DEAD

	Did you attend antenatal clinic in your last pregnancy?	1. Yes 2. No 3. NA (1st pregnancy)		ANCPAST
	Have you ever delivered a baby at home?	1. Yes 2. No 3. NA (1st pregnancy)		DELIVERHOME

4. ANTENATAL CARE IN THE CURRENT PREGNANCY

No	QUESTION	CODING CATEGORIES	CODES	VARIABLE
	Where ANC?			
	How many months pregnant were you when you first went?	|__| months		
	How many times did you go altogether during this pregnancy?	|__|__| times		
During any of your antenatal visits, did the provider do any of the following at least once?				
	Weigh you?	1 = Yes 2 = No 3 = Does not know		
	Measure your height?	1 = Yes 2 = No 3 = Does not know		
	Make you lie down and examine your belly?	1 = Yes 2 = No 3 = Does not know		
	Measure your BP with a cuff?	1 = Yes 2 = No 3 = Does not know		
	Take a sample of your urine?	1 = Yes 2 = No 3 = Does not know		
	Take a sample of your blood for tests?	1 = Yes 2 = No 3 = Does not know		
	Do a syphilis test?	1 = Yes 2 = No 3 = Does not know		
	Do a HIV test?	1 = Yes 2 = No 3 = Does not know		
	Do a HVB test?	1 = Yes 2 = No 3 = Does not know		
	Perform a vaginal examination?	1 = Yes 2 = No 3 = Does not know		
	Give information about VCT/PMTCT services?	1 = Yes 2 = No 3 = Does not know		
	Give information on breastfeeding?	1 = Yes 2 = No 3 = Does not know		
	Give information on contraception?	1 = Yes 2 = No 3 = Does not know		
	Give information on postnatal check?	1 = Yes 2 = No		

		3 = Does not know		
	Give information on pregnancy danger signs?	1 = Yes 2 = No 3 = Does not know		
	Did you have a Tetanus Toxoid Vaccine (TTV) injection in the arm during this pregnancy?	1 = Yes 2 = No 3 = Does not know		
	During this pregnancy were you given, or did you buy any iron tablets or iron syrup?	1 = Yes 2 = No 3 = Does not know		
	Did you go to anyone else for advice during your pregnancy?	1 = Yes 2 = No 3 = Does not know		
	Who did you go to?			
	During this pregnancy, did you take any drugs in order to prevent you from getting malaria?	1 = Yes 2 = No 3 = Does not know		
	Does your household have any mosquito nets that can be used while sleeping?	1 = Yes 2 = No 3 = Does not know		
	Since you got the mosquito net, was it ever soaked or dipped in chemicals to repel mosquitoes or insects?	1 = Yes 2 = No 3 = Does not know		
	When was the last time the net was soaked or dipped in these chemicals?	|__|__| months ago		

5. DELIVERY

No	QUESTION	CODING CATEGORIES	CODES	VARIABLE
	How long did the labour last?	1 = 0 – 6 hours 2 = 7 – 12 hours 3 = 13 – 18 hours 4 = 19 – 24 hours 5 = >24 hours		
	How many hours before the baby was born did the waters break?	1 = <24 hours 2 = >24 hours 3 = Don't know		
	How did the waters smell and look?	1 = No odour/normal odour and clear 2 = Foul smell and green 3 = Don't know		
	How long after the baby's birth did the placenta come out?	1 = <1 hour 2 = >1 hour		
	Did you drink a traditional medicine to assist labour?	1 = Yes 2 = No		
	How many months pregnant were you when you delivered?			[DELIVERYGA]
	Did you experience any complications during this delivery?	1 = Yes 2 = No		[PREGCOMPLICATION]
	If yes, what was the complication?			[TYPEOFCOMPLICATION]
	Who identified this complication?	1= Self 2= Care provider 3= TBA/traditional		[ANTENATALPROBLEM]

		healer 4=Neighbour/ relativelfamily member 5=Not applicable (had no complication)		
	Was this complication an emergency?	1 = Yes 2 = No 3 = Not applicable		[PREGEMERGENCY

6. POSTNATAL CARE AND PRACTICES

No	QUESTION	CODING CATEGORIES	CODES	VARIABLE
	Which of the following best describes what was applied to your baby's cord stump after delivery?	1= Nothing applied 2= Antiseptic 3= Any other material 5=Do not know		[APPLIEDTOCORD]
	How long did it take from delivery to the time your baby was wrapped in any cloth?	1=Immediately after birth and before the placenta was delivered 2=Immediately after birth but after the placenta was delivered 3= Some time after the baby was born 4= Do not know		[WRAPPED]
	How long did it take before your baby was initially bathed?	1. Immediately after delivery 2. Sometime after delivery but within the first day 3=After the first 24 hours 4=Do not know/remember	1_I	[BATH]
	How long did it take before you initially breastfed your baby?	1=Less than one hour after delivery 2=Some hours after delivery but within the first three hours 3=Three hours or more hours after delivery and within the 1st day 4=After the first day 5=Did not breastfeed		
	Were you able to breastfeed your baby with the initial breast milk (colostrum)?	1 = Yes 2 = No	I__I	[COLOSTRUM]
	If the woman did not breastfeed her baby, what was the reason?	1=Advised so by care providers 2=Decided on my own not to breastfeed 3=Baby refused breastfeeding 4=Any other reason	I_I	[NOTBREASTFEED]

	What was the initial food given to your baby?	1=Water 2=Breast milk 3=Animal fat 4=Any other food other than the above mentioned 5=Do not remember	I_I	[INITIALFOOD]

7. KNOWLEDGE OF DANGER SIGNS IN PREGNANCY, LABOUR, DELIVERY AND AFTER DELIVERY

Knowledge of the danger signs in **pregnancy** Do you think the following are danger signs in pregnancy.				
No	QUESTION	CODING CATEGORIES	CODES	VARIABLE
	Vaginal bleeding?	1 = Yes 2 = No		[BLEEDPREGNANCY]
	Blurred vision with or without headache and/or upper central abdominal pain just below the ribs	1 = Yes 2 = No		[BLURRED VISION]
	Fever, that is high body temperature with or without chills	1 = Yes 2 = No		[FEVER]
	Swelling of the face, hands and feet	1 = Yes 2 = No		[OEDEMA]
	Baby in the womb presenting other than by the head after nine months	1 = Yes 2 = No		[MALPRESENTATION]
	Loss of foetal movements for more than two days	1 = Yes 2 = No		[LOSSMOVEMENT]
	Twin pregnancy	1 = Yes 2 = No		(TWIN]
	Abnormal lie of the baby after 36 weeks (nine months)	1 = Yes 2 = No		[ABNORMALLIE]
	Previous Caearean section or vacuum delivery	1 = Yes 2 = No		[LSCSVACUUM]
	Having a rash on your face	1 = Yes 2 = No		[SPOT]

Knowledge of the danger signs in labour or delivery Do you think the following are danger signs in labour or delivery?				
No	QUESTION	CODING CATEGORIES	CODES	VARIABLE
	Severe bleeding during labour or childbirth; that is bleeding excessively to an extent that you feel extremely thirsty or weak	1 = Yes 2 = No		[BLEEDINGINLABOUR]
	Labour more than 12 hours	1 = Yes 2 = No		[PROLONGEDLBOUR]

	Convulsions in labour or childbirth	1 = Yes 2 = No		[ECLAMPSIA]
	Cord coming out of the womb before or during labour	1 = Yes 2 = No		[CORDPROLAPSE]

Knowledge of the danger signs after delivery Do you think the following are danger signs in a woman who has delivered?				
No	QUESTION	CODING CATEGORIES	CODES	VARIABLE
	Failure of the placenta to come out after the baby had been delivered	1 = Yes 2 = No		[RETAINEDPLACENTA]
	Fever, that is high body temperature sometimes associated with chills	1 = Yes 2 = No		[FEVERAFTERDELIVERY]
	Bad smelling vaginal discharge	1 = Yes 2 = No		[SMELLYVAGDISCHARGE]
	Bad smelling vaginal discharge associated with high body temperature	1 = Yes 2 = No		
	Vaginal bleeding more than expected in a woman who has delivered; that is bleeding excessively for days more than expected in a delivered woman	1 = Yes 2 = No		(POSTDELBLEEDING)

Knowledge of the danger signs in the newborn Do you think the following are danger signs in the newborn?				
No	QUESTION	CODING CATEGORIES	CODES	VARIABLE
	Convulsions/spasms/rigidity	1 = Yes 2 = No		[CONVULSIONS]
	Difficult/fast breathing	1 = Yes 2 = No		[DYSPNOEA]
	Very small baby (less than 2.5 kg)	1 = Yes 2 = No		[LBWPREM]
	Lethargy/unconsciousness	1 = Yes 2 = No		[LETHARGY]
	Fever; that is high body temperature that makes the newborn body hot	1 = Yes 2 = No		[BABYFEVER]
	Newborn that cries immediately after delivery	1 = Yes 2 = No		

APPENDIX 9 | On-site-rapid-syphilis test Hexagon Syphilis® test instructions

Hexagon Syphilis® - a 3rd generation screening test for *T. pallidum* antibodies in whole blood (sensitivity: >99%, specificity: >99%).

Hexagon Syphilis

Procedimento

1. Deixar que a amostra, [TEST] e [DIL] cheguem à temperatura ambiente antes de realizar os testes.

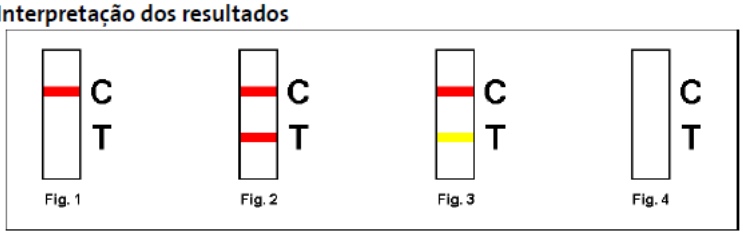
2. Remover o [TEST] da respectiva bolsa e rotulá-lo para identificação do doente.

3. Adicionar **10 µl de soro ou plasma** ou **20 µl de sangue total** (marca preta na pipeta descartável) na janela da amostra (**S**) na extremidade inferior do [TEST].

4. Adicionar **3 gotas plenas** (aprox. 100 µl) de [DIL] à janela da amostra. Evitar bolhas na janela da amostra ao adicionar líquidos.

5. **Ler os resultados aos 5-20 minutos** após o início do teste. Para evitar leituras incorrectas ou resultados inválidos, não ler depois de transcorridos mais de 20 minutos. As amostras fortemente positivas podem apresentar uma linha de teste transcorridos 5 minutos; as amostras limite e negativas só devem ser lidas após 20 minutos de incubação.

Interpretação dos resultados



Negativo (Fig. 1)
Uma única linha de controlo **(C)** vermelho arroxeada aparece na parte superior da janela rectangular de resultado, mostrando que o teste foi executado correctamente.

Positivo (Fig. 2 e 3)
Uma segunda linha de teste (**T**) de cor vermelho arroxeado que aparece na parte inferior da janela rectangular dos resultados, indica um resultado positivo para anticorpos contra *T. pallidum* na amostra.

Mesmo uma linha T fraca indica um resultado positivo (Fig. 3).

Podem ocorrer intensidades diferentes entre as linhas de teste **(T)** e de controlo **(C)**, mas são irrelevantes para a interpretação dos resultados.

Inválido (Fig. 4)
Caso não apareça uma linha de controlo, mesmo que seja visível uma linha de teste, o teste deve ser repetido com um TEST novo.

APPENDIX 10 | INFORMED CONSENT

CONSENTIMENTO INFORMADO

Este consentimento informado destina-se às grávidas internadas para realização do parto na Maternidade do Hospital Dr. Ayres de Menezes, sendo um convite à participação no estudo intitulado:

> **"Análise das causas e factores de risco que contribuem para a morbilidade e mortalidade neonatal em São Tomé e Príncipe - um estudo de caso-controlo"**

Investigadora Principal: Dra. Alexandra Vasconcelos

Promotor: Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa

Este consentimento informado tem duas partes:

- **Página de Informação** (esta informação será lida em voz alta pelo entrevistador)
- **Certificado de Consentimento** (página de assinaturas em que se confirma a aceitação em participar neste estudo)

Será entregue às mães participantes um cartão animado com os dados da investigação assim como a informação de como contactar a qualquer momento o investigador [nome, número de telemóvel STP].

Parte I: Página de Informação

Introdução

O período neonatal - primeiros 28 dias de vida – é o mais vulnerável para a sobrevivência de uma criança. Em São Tomé e Príncipe, a doença no recém-nascido e o risco de morte é percebido como um problema actual estimando-se que elevada percentagem das crianças santomenses morram nos primeiros 28 dias de vida. É, pois, pertinente a compreensão das causas e factores de risco das principais doenças no recém-nascido a fim de identificar prioridades e delinear uma estratégia eficaz à sua redução. Este estudo visa melhorar o actual sistema de saúde materno-infantil.

O que pretendemos fazer?

Casos e controlos: O nosso grupo de investigação propõe estudar as principais causas de doença e morte nos primeiros 28 dias de vida do bebé. Iremos fazer uma entrevista a muitas mães que tiveram um bebé recentemente, fazendo-lhes perguntas sobre como passou a gravidez. Pediremos também para ver o seu boletim de grávida. Quando o seu bebé completar 28 dias de vida iremos telefonar-lhe para saber se passou bem desde que foi para casa. Adicionalmente, algumas participantes, selecionadas de forma aleatória (ao calhas) podem realizar o teste rápido da sífilis (Hexagon syplis test®) para confirmar o resultado do exame feito durante a gravidez no centro de saúde ou fazer por não ter nenhum teste anterior.

Depois de ter ouvido mais informações sobre este estudo e, se concordar, então a próxima coisa que vou fazer é pedir que assine a folha de autorização que me dá permissão para lhe fazer as perguntas do nosso estudo. Antes de decidir, você pode conversar com qualquer pessoa com quem se sinta confortável. Pode haver algumas palavras que não entenda. Por favor, pergunte-me para parar e eu irei explicar. Se só mais tarde se lembrar de alguma dúvida, você pode perguntá-la a mim ou a outro investigador. Deixaremos consigo o nosso número de telemóvel caso surja alguma dúvida e precise de nos falar.

Participação voluntária: A participação é voluntária. Deve saber que não tem que responder a qualquer pergunta ou autorizar a colheita de sangue caso não queira e pode recusar a sua participação a qualquer momento. Você pode optar por dizer não e todos os serviços de saúde que você e sua família recebem neste hospital/centro de saúde não vão mudar.

Tipo de Investigação

Iremos ler em voz alta as perguntas do questionário e as suas respostas serão escritas ou registadas em papel ou computador. Durante a entrevista, se não desejar responder a qualquer das perguntas, pode dizer e o entrevistador vai passar para a próxima pergunta. Iremos também pedir para consultar o seu boletim de grávida. A informação registada é confidencial, e mais ninguém, excepto o entrevistador/investigadora terá acesso às suas informações.

Selecção dos Participantes: o convite a participar neste estudo é dirigido à parturiente e/ou qualquer recém-mamã que tenha um bebé sem doença/com doença/ou que tenha tido um bebé que morreu antes de completar o 28º dia de vida.

Duração: A sua participação levará cerca de 30 minutos do seu tempo.

Quais são os riscos envolvidos caso participe neste estudo? Não existe risco para a saúde. Poderá partilhar connosco algumas informações pessoais e confidenciais ou poderá sentir-se desconfortável falando sobre alguns dos temas.

Quais são os benefícios do estudo? Não há benefício imediato e directo para o seu bebé ou para você, mas a sua participação permitirá ajudar a saber mais sobre as necessidades das grávidas e dos recém-nascidos e assim esperamos contribuir para uma melhoria da saúde materno-infantil de STP.

Confidencialidade: Nada do que nos vai dizer será dito a alguém fora da equipa de pesquisa, e nada vai ser atribuído ou identificado pelo seu nome ou do bebé. No final do estudo, iremos partilhar o que aprendemos com o Ministério de Saúde de São Tomé e Príncipe. Iremos também publicar os resultados em revistas médicas, a fim de que outras pessoas interessadas possam aprender com a nossa investigação.

Direito a recusar: Você pode optar por não participar neste estudo. A escolha em participar ou não, não vai afectar de qualquer forma o seu ou tratamento futuro do seu bebé ou família neste Hospital/Centro de Saúde. Você, bebé e família terão todos os benefícios que são disponíveis neste Hospital/Centro de Saúde. Pode deixar de participar neste estudo a qualquer momento que desejar, sem qualquer um de vocês perder qualquer um dos seus direitos.

Quem contactar: Se tiver quaisquer dúvidas pode perguntá-las agora ou mais tarde, mesmo após o início do estudo. Se quiser fazer perguntas depois, você pode entrar em contato com a equipa de investigadores cujo contacto está no cartão que agora lhe entregamos.

Esta proposta foi revista e aprovada pelo Ministério de Saúde de São Tomé e Príncipe.

□□□□□.□□□□.□□.□□

Nº de entrada: _____

PARTE II: Formulário do Consentimento Informado

PÁGINA DE ASSINATURAS

"Análise das causas e fatores de risco que contribuem para a morbilidade e mortalidade neonatal em São Tomé e Príncipe - um estudo de caso-controlo"

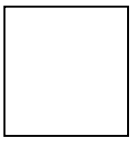
Eu, abaixo-assinado, fui convidada a dar o meu consentimento em participar neste estudo que consiste em responder a algumas perguntas sobre mim, sobre a gravidez e o meu recém-nascido. Compreendi a explicação que me foi fornecida, por escrito e verbalmente, da investigação que se tenciona realizar, para qual é pedida a minha participação.
Tive a oportunidade de fazer perguntas sobre o estudo e todas as perguntas que fiz foram respondidas. Tomei conhecimento de que, de acordo com as recomendações da Declaração de Helsínquia, a informação que me foi prestada versou os objetivos, os métodos, os benefícios previstos, os riscos potenciais e o eventual desconforto. Além disso, foi-me afirmado que tenho o direito de decidir livremente aceitar ou recusar a todo o tempo a minha participação no estudo. Sei que se recusar não haverá qualquer prejuízo na assistência que me é prestada.
Foi-me dado todo o tempo de que necessitei para refletir sobre esta proposta de participação. Nestas circunstâncias, decido livremente aceitar participar neste projeto de investigação, tal como me foi apresentado pela investigadora.

Nome: _____
Assinatura: _____
Local: _____ Data:___/_____ /_____

Testemunha – (se iletrada ou menor de idade)

Eu testemunhei a leitura precisa do formulário de consentimento à parturiente ou mãe/representante legal, e que esta teve a devida oportunidade de fazer perguntas. Confirmo que o indivíduo deu o seu consentimento livremente.
Nome e assinatura da Testemunha:
Nome: _____
Assinatura: _____

Impressão Digital (participante)



Declaração do investigador

Eu li com precisão a folha de informação ao potencial participante, e com o melhor de minha capacidade assegurei-me que a pessoa entende que a seguir irá ser feito a todos os participantes do estudo:

1. **uma entrevista para responder a um questionário**
2. **consultar o boletim da grávida**
3. **realização do teste rápido de diagnóstico da sífilis por colheita de duas gotas de sangue periférica de sangue (riscar se não aplicável)**
4. **receber um telefonema da investigadora após os 28 dia de vida do bebé para saber se esteve bem após ter tido alta da maternidade**
5. **publicação dos dados analisados desde que o anonimato seja mantido**

Confirmo que o mesmo teve a oportunidade de fazer perguntas sobre o estudo e todas as perguntas feitas foram respondidas corretamente e com o melhor de minha capacidade. Confirmo que o indivíduo não foi coagido a dar o seu consentimento e o consentimento foi dado livremente e voluntariamente.
Nome de quem leu o consentimento informado: _____
Assinatura: _____

APPENDIX 11 | ETHICAL CLEARANCE

REPÚBLICA DEMOCRÁTICA DE S. TOMÉ E PRÍNCIPE

MINISTÉRIO DA SAÚDE

(Unidade - Disciplina – Trabalho)

DECLARAÇÃO

A Direcção Clínica do Hospital Dr. Ayres de Menezes da República Democrática de São Tomé e Príncipe para os devidos efeitos de informar a Fundação para a Ciência e a Tecnologia (FCT), vem através do seu Director, abaixo-assinado, confirmar que aceita ser a instituição de acolhimento onde decorrerão os trabalhos de investigação em saúde nacional (SFRH/BD/117037/2016 do projecto de doutoramento em Medicina Tropical do Instituto de Higiene e Medicina Tropical (IHMT) da Dr.ª Alexandra Maria Pinto de Castro Vasconcelos, Médica Pediatra de nacionalidade Portuguesa. Este estudo clínico teve autorização ética formal do Ministério da Saúde de São Tomé e Príncipe.

O Hospital Dr. Ayres de Menezes é uma instituição hospitalar que garante as condições necessárias ao bom desenvolvimento do programa de trabalho. O estudo clínico nesta instituição será tutelado pelo Dr. Nelson Bandeira sendo o Prof. Doutor João Luís Batista o co-orientador da Dra. Alexandra Vasconcelos que irá acompanhar, não directamente, o decorrer desta investigação em São Tomé e Príncipe.

São Tomé, 19 de Julho de 2017.

HOSPITAL DR. AYRES MENEZES

O Director Clínico,

Dr. Martinho Santos

DIRECÇÃO CLINICA

Hospital Dr. Ayres de Menezes de S. Tomé – C.P.373-Telef. 2223720/2221222/Fax: 2221233

APPENDIX 12 | RESEARCH AND FIELD WORK PHOTOGRAPHS

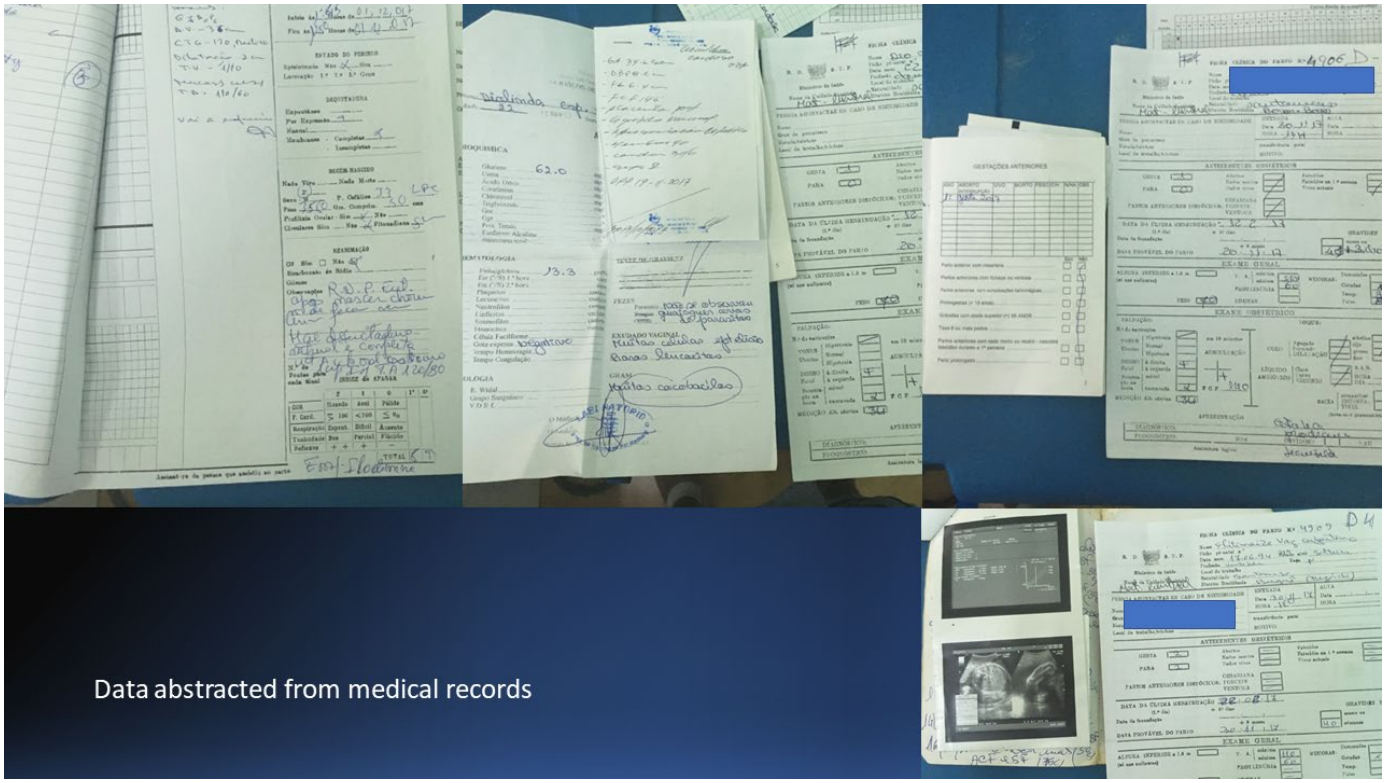
LOCAL COLABORATION TEAM

- Nelson Bandeira, MD Obstetrics/Gynaecology Director
- Swasilanne Sousa, MD Paediatric Department Director
- Head Chief-Nurse Paulina Oliveira of HAM Maternity Unit
- Midwives and nurses of HAM maternity unit
- Medical doctors
- Lab technicians

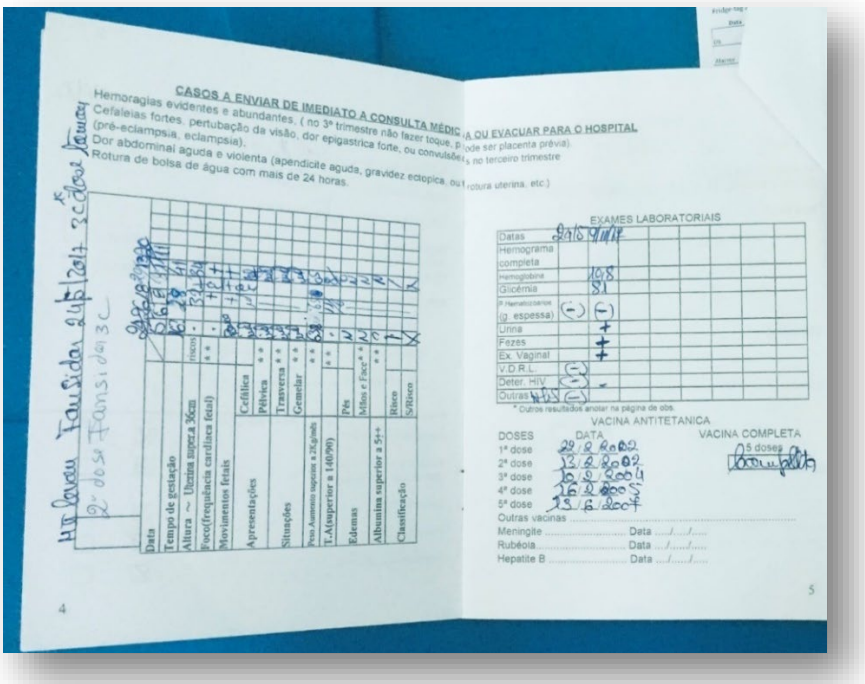




Photos | personal photos_Alexandra Vasconcelos©



Antenatal pregnancy card/bulletin



Photos | personal photos_Alexandra Vasconcelos©

APPENDIX 13 | Children under-two years old admissions at the HAM Paediatric ward (2015-2016)

18º Congresso Nacional de Pediatria, Centro de Congressos Alfândega do Porto. 25-27th October, Portugal.

Available at: https://www.spp.pt/UserFiles/file/18_CNP/SUPLEMENTO_2017.pdf

PD-114 - (18SPP-4526) - INTERNAMENTOS EM IDADE PEDIÁTRICA NO HOSPITAL CENTRAL DE SÃO TOMÉ E PRÍNCIPE (2015-2016)

Ana Sequeira[1]; Alexandra Vasconcelos[2]; Swasilanne Sousa[3]; Feliciana Almeida[3]; Filomena Pereira[2]; Maria Do Céu Machado[4]

1 - 1.Serviço de Pediatria Médica, Departamento de Pediatria, Hospital de Santa Maria - Centro Hospitalar de Lisboa Norte, EPE; 2 - 2.Unidade de Clínica Tropical - Global Health and Tropical Medicine, Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa; 3 - 3.Serviço de Pediatria do Hospital Dr. Ayres de Menezes, República Democrática de São Tomé e Príncipe; 4 - 4.Professora de Pediatria da Faculdade de Medicina de Lisboa, Universidade de Lisboa

Introdução e Objectivos: São Tomé e Príncipe é um país africano em desenvolvimento com uma população jovem; 42% têm idade inferior a 15 anos. A taxa de mortalidade infantil em 2014 foi de 35 por 1.000 nascidos vivos.

Objetivos: 1) Análise dos motivos de internamento e características sócio-demográficas das crianças admitidas e 2) identificação das causas de mortalidade.

Metodologia: Estudo retrospetivo e descritivo de processos clínicos das crianças com idade ≤2 anos de vida internadas, entre agosto 2015 a maio de 2016, num hospital central com recursos limitados.

Resultados: Foram internadas 1063 crianças, 56% (n=597) do género masculino. A idade mediana foi de 10 meses [mín. 3 dias–máx. 24 m], sendo 5% (n=52) recém-nascidos. No período neonatal, os principais diagnósticos foram sépsis (n=14; 27%), bronquiolite aguda (n=8; 15%), tosse convulsa (n=5; 10%), icterícia (n=3; 6%), a que se seguiram malformações congénitas, pneumonia, onfalite, gastroenterite aguda (GEA), má progressão ponderal e adenite.

Os principais diagnósticos nas crianças (≥1m-≤2 anos) foram: GEA (n= 268; 25%), pneumonia (n=235; 22%), bronquiolite aguda (n=219; 21%), desnutrição (n=35; 3%) e infeções da pele e tecidos moles (n=32; 3%). Registaram-se 11 óbitos: 8 casos de GEA (3 crianças com co-morbilidades), 2 de pneumonia e 1 de sépsis neonatal.

Conclusões: As principais causas de admissão global foram pneumonia e GEA, assim como de mortalidade, as quais são também identificadas como as principais causas de morbimortalidade em crianças até aos 5 anos em vários países africanos. Apesar da limitação temporal da recolha de dados e frequência de registos incompletos nos processos clínicos, esta análise poderá fornecer suporte para desenvolver estratégias com o intuito de continuar a melhorar a saúde infantil em São Tomé e Príncipe.

Palavras-chave: morbimortalidade, hospital com recursos limitados, São Tomé e Príncipe

APPENDIX 14 | On-site-rapid-syphilis-test Hexagon Syphilis® results

Abstract for the poster with discussion communication.

18º Congresso Nacional de Pediatria, Centro de Congressos Alfândega do Porto. 25-27th October, Portugal.

Available at: https://www.spp.pt/UserFiles/file/18_CNP/SUPLEMENTO_2017.pdf

POSTERS COM DISCUSSÃO

PD-137 - (18SPP-4492) - WHY, WHEN AND WHERE DO NEWBORNS NOT ONLY GET SICK BUT ALSO DIE IN SÃO TOMÉ AND PRÍNCIPE? – A CASE-CONTROL STUDY

Alexandra Vasconcelos[1]; Rita Coelho[2]; Ana Miranda[2]; Ana Sequeira[3]; Swasilanne Sousa[4]; Nelson Bandeira[4]; João Luís Baptista[5]; Filomena Pereira[1]; Maria Do Céu Machado[6]

1 - Unidade de Clínica Tropical - Global Health and Tropical Medicine, Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa; 2 - Departamento de Pediatria, Hospital Prof. Doutor Fernando Fonseca, EPE; 3 - Departamento de Pediatria, Hospital de Santa Maria (CHLN), Centro Académico de Medicina de Lisboa; 4 - Hospital Dr. Ayres de Menezes, República Democrática de São Tomé e Príncipe; 5 - Professor Convidado da Faculdade Ciências da Saúde, Universidade da Beira Interior; 6 - Professora de Pediatria da Faculdade de Medicina de Lisboa, Universidade de Lisboa

Introdução e Objectivos: Neonatal deaths in São Tomé and Príncipe account for about 43% of all under-5 deaths, major gaps exist in its understanding.

Objectives: Identify ante-intra-postpartum risk factors and analyse characteristics of neonatal morbi-mortality.

Metodologia: Case-control study: stillbirths and sick newborns (NB) with ≥32 week´s gestation or ≥1500g were eligible cases. Those healthy ≥28 days were controls. Results presented are from first phase recruitment from mothers' and NB medical records, supplemented with a questionnaire applied by the investigator, data was analyzed using SPSS 23. Informed consent was obtained from 132/675 mothers enrolled, 134 NB (2 twins) observed. Thirty five cases and 41 controls NB were followed-up.

Resultados: Pregnant women medium age was 26 years (23% adolescents), 23% without antenatal care. Primary education was attended by 57%, secondary by 63%, 7% were illiterate. One positive test was found of a total of 96 on-site-rapid-syphilis-test undertaken. HIV or malaria were not detected, three infected with HBV. Newborns (134) morbi-mortality: 10 preterm, 12 birth asphyxia, 30 risk of neonatal and 8 invasive infections, 8 fetal growth restriction, 5 microcephaly, 4 minor congenital anomalies and one death in the first 24h of life due to congenital lung anomaly. Comparing cases (35) and controls (41) indicated that low birth-weight (<2500g), meconium and caesarean section were associated with morbidity. No deaths verified in the 76 babies' followed-up.

Conclusões: Although morbidity in the NB studied is high (59%), the small number enrolled does not allow to draw more conclusions. However, at the completion of this study we will be able to do so and to design an intervention algorithm in order to achieve peri-neonatal morbi-mortality reduction.

Palavras-chave: neonatal morbi-mortality, São Tomé and Príncipe, ante-intra-postpartum risk factors



HEXAGON SYPHILIS®

96

on-site-rapid-syphilis tests performed

1 POSITIVE TEST

