



**Escola Nacional  
de Saúde Pública**

UNIVERSIDADE NOVA DE LISBOA

**Measuring the impact of influenza vaccination national strategy  
among the at risk Portuguese population**

Doutoramento em Saúde Pública

**Ausenda Machado**

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## **Measuring the impact of influenza vaccination national strategy among the at risk Portuguese population**

Tese apresentada para cumprimento dos requisitos necessários à obtenção do grau de Doutor em Saúde Pública, realizada sob a orientação científica de Professor Doutor Baltazar Emanuel Guerreiro Nunes Bravo Nunes e da Professora Amparo Larrauri.

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## Abstract

Yearly seasonal influenza vaccine is recommended to individuals with chronic conditions or aged  $\geq 65$  years (high-risk group). However, for these high-risk individuals, the vaccine coverage has been lower than targeted, vaccine effectiveness may be altered by age or presence of chronic conditions and the impact of the vaccination strategy is still unknown.

With focus in the high-risk group, this thesis aimed contributing to the national influenza strategy by providing information on i) influenza vaccine coverage and associated factors; ii) vaccine effectiveness and iii) impact of influenza vaccination strategy at population level.

Results indicate that the proportion of individuals with vaccine uptake for four consecutive seasons was only 27%. Age, having a chronic condition and use of health care were positively associated to vaccine uptake. Vaccine effectiveness was estimated in 52% against medically-attended influenza and 32% against influenza hospital admissions in the ones aged  $\geq 65$  years. The tested hypothesis of an effect modification of the vaccine by age or chronic conditions, was inconclusive, probably due to lack of power. The impact of influenza vaccination strategy indicate that on average, during the period 2014/15-2017/18, the strategy averted 715 primary care medically attended influenza; 1833 hospitalizations and 383 intra-hospital.

The influenza vaccine strategy had consistent and positive benefit in the high-risk population. To maximize the impact, efforts should be conducted to increase the vaccine coverage and the results of this thesis could be used to design targeted strategies. The continuous monitoring of the vaccine effectiveness and population impact could contribute in this effort.

Keywords: influenza, influenza vaccine program, vaccine effectiveness, vaccine coverage, impact of vaccine program



## Resumo

A vacina contra a gripe é recomendada anualmente a indivíduos alto-risco de complicações, nomeadamente aqueles com doenças crónicas ou idade  $\geq 65$  anos. Contudo, a cobertura da vacina neste grupo de alto-risco é inferior à meta estabelecida, a efetividade pode ser modificada pela idade e pela doença crónica e o impacto da estratégia de vacinação é desconhecido.

Com foco nos indivíduos de alto-risco, esta tese pretendeu contribuir para a estratégia de vacinação contra a gripe fornecendo informações sobre a i) cobertura vacinal e fatores associados, ii) efetividade da vacina e iii) impacto a nível populacional da estratégia de vacinação.

Os resultados indicam que a proporção de indivíduos com toma da vacina nas 4 épocas foi de 27%. A idade, ter doença crónica e utilização de cuidados de saúde estavam positivamente associados à toma de vacina. A hipótese de modificação de efeito da vacina pela idade e comorbilidades foi inconclusiva, decorrente provavelmente da falta de potência do estudo. ). A efetividade da vacina foi estimada em 52% na redução de consultas e em 32% na redução de hospitalizações nos indivíduos com  $\geq 65$  anos. Por último, a estratégia de vacinação preveniu em média, durante o período em análise (2014/15-2017/18), 715 consultas, 1833 hospitalizações e 383 óbitos intra-hospitalares.

A estratégia de vacinação contra a gripe teve benefícios positivos na população de alto-risco. Para maximizar este impacto devem ser realizados esforços para aumentar a cobertura e os resultados desta tese podem ser importantes no delineamento de intervenções direcionadas. A contínua monitorização da efetividade e do impacto da vacina na população poderiam contribuir para esse objetivo.





## List of Tables

Table 1 Summary IV uptake statistical significant associated factors (country-specific Odd-ratio OR point estimates) .....	28
Table 2. Summary of ecologic models main features used for interventions (adapted from Sallis et al. (124) .....	32
Table 3. Summary results of influenza vaccination program impact on medically attended influenza, hospitalizations and death .....	44
Table 4. List of independent variables used in study 1 and study 2 .....	52
Table 5. Potential confounding factor collected in EuroEVA (study 3) and EVAHospital (study 4) .....	58
Table 6. List of ICD 9 <sup>th</sup> and 10 <sup>th</sup> version codes for SARI.....	62
Table 7. List of ICD 9 <sup>th</sup> and 10 <sup>th</sup> version codes for chronic conditions .....	63
Table 8. Data sources used for impact studies (study 5 and study 6).....	64
Table 9. Pooled VE resulted from the IMOVE multicenter primary care based study.....	67
Table 10. Distribution of circulating influenza (sub)types in Portugal, all ages .....	67
Table 11. Meta analysis type/subtype IVE estimates for ≥65 years and <65 years.....	68
Table 12. Distribution (%) of circulating influenza type/subtypes in Portugal in hospital settings .....	68

## List of Figures

Figure 1. Thesis structure .....	16
Figure 2. Evolution of immunization programs (18) .....	21
Figure 3. Mapp of influenza vaccination recommendation in Europe: A) children, B) pregnant women, C) chronic diseases and D) elderly. source: European Health Information Gateway (98) .....	24
Figure 4. Influenza Vaccine Coverage in the WHO-European region in the 2015/16 season.....	26
Figure 5. Schematic representation of vaccine effects represented by Hanquet et al. (15) .....	40
Figure 6. Conceptual model of the thesis .....	45



# List of Abbreviations

ADL -Activities Of Daily Living  
ARIMA - Autoregressive Integrated Moving Average  
CHS - Centro Hospitalar de Setúbal  
CHULC - Centro Hospitalar Universitário Lisboa Central  
CI – Confidence Interval  
COPD - Chronic obstructive pulmonary disease  
DAG -directed acyclic graphs  
EC -Ethical Committee  
EU – European Union  
EuroEVA - Efetividade da Vacina Antigripal na Europa  
EVAHospital - Efetividade da Vacina Antigripal contexto Hospital  
GP - General Practitioner  
H - Hemagglutinin  
HTA - Hypertension  
HCW - Health Care Worker  
IADL - Instrumental Activities Of Daily Living  
ICD – International Classification of Diseases  
ICU - intensive care unit  
ILI - Influenza Like Illness  
I-MOVE - Influenza-Monitoring Vaccine Effectiveness  
INS2014- 5<sup>th</sup> National Health Survey  
INSA - Instituto Nacional de Saúde Doutor Ricardo Jorge  
INSEF2015 -1<sup>st</sup> National Health Examination Survey-  
IRE – Influenza-Related events  
ISCED - International Standard Classification of Education  
IV- Influenza Vaccine  
IVE – Influenza Vaccine Effectiveness  
IVS - Influenza Vaccine Strategy  
N - Neuraminidase  
NAE – Number of Averted Events  
NNV – Number Needed to Vaccinate  
NUT - Nomenclatura das Unidades Territoriais para Fins Estatísticos  
OR - odds ratios  
PDS -Health Data Platform  
PF – Prevented Fraction

PSU - Primary Sampling Units  
REDCap - Research Electronic Data Capture  
SARI – Severe Acute Respiratory Illness  
TND - Test Negative Design  
VC- Vaccine Coverage  
VPD - Vaccine Preventable Diseases  
WHO - World Health Organization

# Table of Content

Agradecimientos .....	i
Abstract .....	iii
Resumo .....	v
List of Tables .....	vii
List of Figures .....	vii
List of Abbreviations .....	ix
1 Introduction .....	13
2 Background .....	17
2.1 Influenza: the disease and associated burden .....	17
2.2 Influenza vaccines and vaccination strategies .....	21
2.3 Influenza vaccine coverage .....	24
2.4 Influenza vaccine effectiveness .....	33
2.5 Impact of influenza vaccination strategy .....	39
2.6 Conceptual model of the thesis .....	44
3 Study population, research questions and objectives .....	47
4 Methods .....	49
4.1 Influenza vaccine coverage and associated factors .....	49
4.2 Influenza vaccine effectiveness .....	54
4.3 Impact of the influenza vaccination strategy .....	59
4.4 Ethical and data protection issues .....	70
5 Results .....	71
5.1 Influenza vaccine coverage and associated factors .....	71
5.2 Influenza vaccine effectiveness .....	95
5.3 Impact of influenza vaccination strategy .....	131
6 Discussion .....	166
6.1 Main findings .....	166
6.2 Strengths and limitations .....	169
6.3 Implications for public health practice and research .....	172
7 Conclusions .....	176
8 References .....	178
9 Annex .....	197
9.1 Questionnaires .....	197
9.2 Ethical and Data Protection clearance .....	201



# 1 Introduction

Influenza is a viral respiratory disease that circulates on a yearly basis. For the majority of the population, the virus circulation is associated to mild symptomatic disease epidemics. However, in individuals with frail health status due to age or chronic disease(s), influenza infections can exacerbate pre-existing conditions, leading to severe outcomes such as hospitalizations or death. This is an extreme situation but can have an absolute impact of considerable magnitude (1–6). Systematic review results suggest that older adults aged 65 and more years, children with less than 5 years, individuals with underlying conditions and pregnant women are a high-risk group of complications due to influenza infection (7).

Since the 1950's an egg propagated vaccine against influenza is available (8). Influenza vaccination has been considered the main public health measure for influenza control and its role in reducing the risk of developing the disease and the occurrence of their complications is widely recognized (9). For the high-risk population with higher risk of post-infection complications, the influenza vaccine (IV) uptake is recommended on a yearly basis (9) in order to reduce the disease and their related complications.

Some influenza vaccination strategies rely on vaccinating all individuals, while others target specific population groups (10). In Portugal, a risk-based strategy has been in place, where annual recommendation include among others the older adults with 65 and more years and individuals with chronic conditions (11). The vaccine is offered free of charge, since 2012 for older adults with 65 and more years (12), and since 2016 for individuals with diabetes) (13) or is reimbursed (for people with other comorbidities). Also, specific awareness campaigns using different communications strategies have been in place in Europe (14).

As any other vaccine, influenza vaccine provides both direct effect on vaccinated individuals, by reducing the risk of infection, but also indirect effect on unvaccinated individuals, by reducing the susceptible population and thus the transmission of the virus (15–17). As such, besides individual benefit obtained by the vaccine, there is a population effect provided by the vaccination program. This overall population based effect is observed by the reduction of the influenza burden. To achieve high vaccine and vaccination effect, it is important to have high population coverage and vaccine effectiveness (16).

As stated by Chen and Orenstein (1996) (18) "*surveillance on several aspects of an immunization program are needed to assure its optimal performance*". Translating into the national influenza vaccination program, it is important to monitor vaccine coverage, effectiveness and the impact of the vaccination program.

Influenza virus and available vaccines have their own specificities. Given the high mutation rate of the influenza virus and the low sustained vaccine induced immunity, the vaccine is reformulated every year, posing a significant methodological, production and operational distribution and immunization of the population challenges. These challenges are thus transferred on the vaccination monitoring.

In Portugal, the vaccine coverage (VC) has been monitored on a yearly basis. The IV coverage in the community-dwelling older adults with 65 and more years was around 50% for several years (19) and increased to 60% in the 2017/18 season (20). The vaccine coverage in institutionalized older adults with 65 years and more has been higher, more than 90%. In individuals with underlying health conditions, IV coverage was 30% until 2014/15 season (21) and increased into 40% in the 2017/18 season. Although this positive increment in high-risk populations, it is still far from the IV coverage target of 75%, set by the World Health Organization (WHO) and the European Commission (EU) (22). A survey conducted in 2013 in mainland Portugal, found that some of the target group individuals do not recognize themselves as belonging to risk-group or the benefit of IV uptake (23). On the other hand, and although the extend of coverage is undetermined, there are individuals that are vaccinated on a regular basis. Identifying factors that predict (regular) vaccination is necessary to promote targeted vaccination strategies and increase the vaccine uptake.

In relation to influenza vaccine effectiveness (IVE), international efforts have been in place to determine the early and end of season vaccine effect in reducing influenza (24–26). In Portugal, since 2008, a test-negative design has been yearly implemented in order to assess IVE against medically attended influenza in primary care (27). Maintaining such a system and providing annual IVE at national level is considered key in the influenza burden management (28). Moreover, and given the need for estimates with good precision, multicentric studies have been important in obtaining annual evidence of the vaccine protection (24). Even though this was an important step towards the vaccine evaluation in our country, other effectiveness studies need to be conducted. Namely, there is need to understand how protective is the vaccine in preventing more severe cases of influenza that require hospitalizations. In addition, given the observational nature of effectiveness studies, sound epidemiological methods



need to be used to adjust for potential confounding and reduce biased IVE estimates (29).

Finally, there is limited data on the impact at population level of the national influenza vaccination strategy. Although, no consensus definition exists on the impact of vaccination program (15,17), it is agreed that it is an important indicator to describe the benefit of this public health intervention (17). Transmission dynamic models (10) or ecologic approaches (30,31) have been used to estimate the impact of vaccination programmes on influenza-related outcomes, such as consultations, hospitalizations and mortality. These impact indicators have been used for planning and to evaluate the success of the influenza vaccine programme (3). However, until now, most of the impact of the vaccine strategy at population level has been limited to the United States (US) experience, while few European results on this subject have been reported (32,33).

This thesis addresses the vaccine coverage, vaccine effectiveness and vaccination impact components of the Portuguese influenza vaccination strategy (Figure 1). For these three key components of the IV program, six studies were developed (two studies per component).

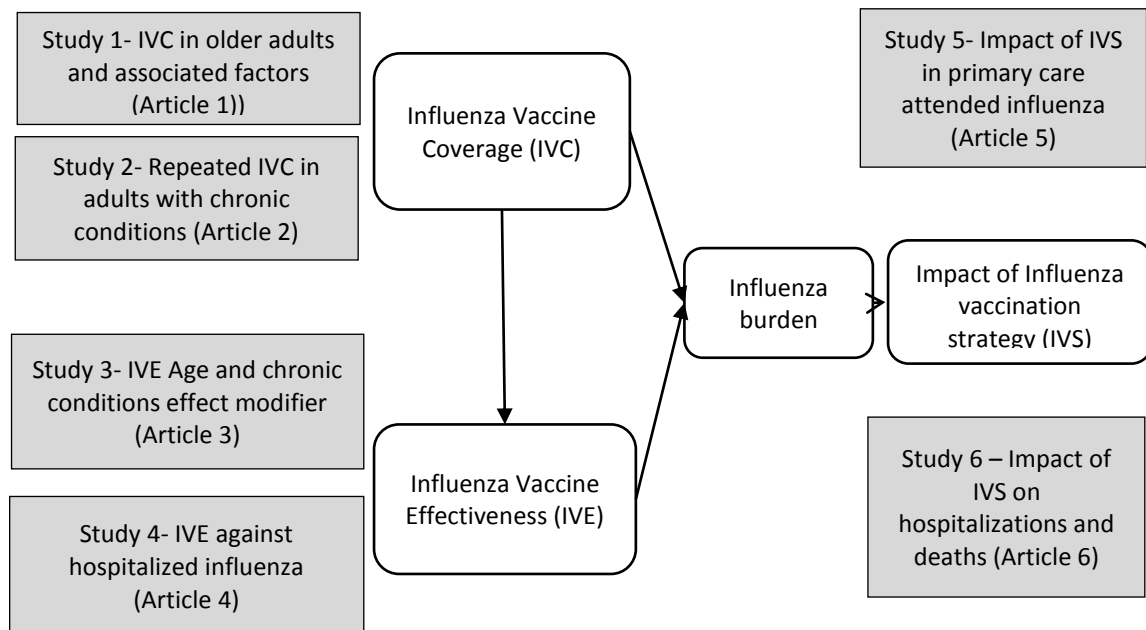
Study 1, addresses the IV uptake within the population with 65 and more years and the factors associated to IV uptake, using the Social Ecologic Model as framework. (Article 1)

Study 2, refers to repeated vaccination and associated factors, taking in consideration both adults with chronic condition and older adults with age between 65 and 74 years. (Article 2)

Study 3 and 4 were dedicated to the direct effect of the vaccine in real world conditions. While, study 3 (Article 3) addresses the potential of age and chronic conditions as an effect modifier of IVE against influenza confirmed primary care consultations, study 4 (Article 4) describes the implementation and results of IVE against hospitalizations, in the population aged 65 years or more, implemented in Portugal during 2015 to 2018.

Study 5, is focused on adults with 65 and more years and reports the results of the implementation of a harmonized protocol to measure the impact of influenza vaccination program on medically-attended influenza in three European countries, namely, Portugal, Spain and Netherlands. (Article 5)

Study 6 addresses the high-risk population (adults with 65 and more years and < 65 years with a chronic condition) and provides the results on the impact of the influenza vaccination program on severe influenza outcomes (Article 6).



**FIGURE 1. THESIS STRUCTURE**

**Article 1.** Machado A, Santos AJ, Kislaya I, Larraury A, Nunes B. Understanding influenza vaccination among Portuguese elderly: the social-ecological framework. *Health Promotion International*. 2020. daaa011, <https://doi.org/10.1093/heapro/daaa011>.

**Article 2.** Machado A, Kislaya I, Santos AJ, Gaio V, Gil AP, Barreto M, Namorado S, Antunes L, Matias Dias C, Nunes B. Factors associated to repeated influenza vaccination in the Portuguese adults with chronic conditions. *Vaccine*. 2018 Aug 23;36(35):5265-5272. doi: 10.1016/j.vaccine.

**Article 3** Machado A, Leite A, Larraury A, Nunes B on behalf of the EuroEVA team. Is there effect modification of influenza vaccine effectiveness by age and chronic conditions?. (submitted to *Pharmacoepidemiology and Drug Safety*).

**Article 4.** Machado A, Gomez V, Panarra A, Poças J, Corte-Real R, Peres MJ, Nunes B on behalf of EVA Hospital study. Implementing an influenza vaccine effectiveness against hospitalized influenza study in Portugal. (submitted to *Acta Médica Portuguesa*).

**Article 5.** Machado A, Mazagatos C, Dijkstra F, et al. Impact of influenza vaccination programmes among the elderly population on primary care, Portugal, Spain and the Netherlands: 2015/16 to 2017/18 influenza seasons. *EuroSurveillance*. 2019;24(45):1900268. doi:10.2807/1560-7917.ES.2019.24.45.1900268

**Article 6.** Machado A, Kislaya I, Larrauri A, Matias Dias C, Nunes B. Impact of national influenza vaccination strategy in severe influenza outcomes among the high-risk Portuguese population. *BMC Public Health* **19**, 1690 (2019) doi:10.1186/s12889-019-7958-8.

## 2 Background

### 2.1 Influenza: the disease and associated burden

Influenza is a respiratory infection caused by a RNA virus with segmented genome. There are four types of influenza virus (A, B, C and D), that can be further (sub)typed according to virus specificities. All this variety of influenza types and subtypes can affect different animal hosts, from birds to mammals (34).

In what relates to humans, only A and B virus are responsible for the yearly seasonal epidemics that mainly occur in the winter season. Type A virus can be classified according to two proteins, hemagglutinin (H) and neuraminidase (N), both responsible in the virus infection and propagation. There are 16 different types of H (H1 to H16) and 9 N (1 to 9) (35,36). Influenza A subtype H1, H2 and H3 and N1 and N2 are responsible for epidemics in humans; the remaining subtypes are found in birds and some mammals (37). Influenza B virus are also responsible for epidemics and two lineages have been circulating in human, namely Victoria and Yamagata (38).

Influenza virus are named according to virus type, the host of origin, geographical origin, strain number and year of isolation (39). For human-origin viruses, no host of origin designation is given and for influenza A viruses, the hemagglutinin and neuraminidase antigen is described in parentheses (e.g., (H1N1), (H5N1) (39).

Both A and B virus, present a high genetic evolutionary capacity, allowing them to escape the host immune system. These small but cumulative genetic processes, referred as antigenic drift, are responsible for the seasonal epidemics. Another important genetic process, that only occurs with type A virus, is the gene reassortment (34). This process allows the virus to combine with different subtypes into a new subtype. This process is called antigenic shift and if a subsequent viable human-to-human transmission is provided, this new subtype can cause a pandemic (34).

The annual pattern of the seasonal influenza epidemics varies with the geographical location: between December-March in countries in the northern hemisphere; April-September in countries in the southern hemisphere and bi-annual circulation in tropical and sub-tropical countries (37,40,41). This differential pattern are in some extend due to some contributing factors such as lower ventilation and higher population crowding during winter periods (40). Also, weather conditions such as temperature and humidity which are described as influencing the survival of the virus, its ability to spread in the air and the susceptibility of the host (42).

The primary person-to-person virus transmission occurs via viral spread during coughing or sneezing (41,43) and a secondary transmission can occur by direct

contact with patient skin or contaminated surfaces(37,44). The reproduction number of seasonal influenza was estimated in 1.28, i.e., one infectious case can generate on average 1.28 subsequent cases in susceptible population (45). With an incubation period of approximately 1 to 2 days, influenza infection symptoms include fever, myalgia, headache, sore troath, cough and shortness of breath (37,40).

Seasonal influenza epidemics are characterized by the increase in influenza infection incidence above a non-epidemic baseline. Seasonal epidemics usually have a sharp increase of the incidence, with an observed peak after 2 to 3 weeks. Overall duration of seasonal epidemics is 5 to 10 weeks.

Most countries have clinical influenza surveillance systems in place (46–50) and can detect the epidemic starts, maximum and ends. Some, Portugal included, also have an integrated system that includes the detection of virus in circulation, allowing the characterization of the virus type and subtype dominant in that season (51–53). This surveillance has been of extreme importance in detecting epidemics activity and has been pointed out as added value in countries from Western Pacific Region when deciding the introduction and evaluation of influenza vaccine (54). In seasons with high activity, these systems can alert health authorities of the potential impact on health services. In systems that incorporate other epidemiological indicators, as admissions in intensive care unit and/or medicine and all-cause or pneumonia and influenza mortality, it has been possible to access influenza severity (55).

In most seasons and for the majority of the population, influenza epidemics cause mild symptomatology disease. Seasonal influenza attack rate varies with age group, being higher in children (12.7%) and adults with 65 and more years (7.2%) (56). Considering the fraction of asymptomatic infected individuals, that according to a meta-analysis could range from 16% in outbreaks investigation to 65%-85% across epidemics (57), the overall influenza impact is considerable higher.

In addition, for a group of individuals, influenza virus can complicate into more severe disease and outcomes. Individuals with chronic disease, influenza infection can exacerbate these underlying conditions, posing a significant risk of developing more severe outcomes. The relation between influenza infection and exacerbation of chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD) is well recognized (58). In addition, there is considerable evidence that influenza can aggravate and complicate pre-existing cardiovascular diseases (59). In a systematic review and meta-analysis, Coleman et al. (7) found that in developed countries, older age, having diabetes, an immunocompromised disease or condition,

chronic renal, cardiovascular, and kidney disease, were all risk factors for influenza related hospital admission, intensive care, and/or death.

Influenza burden is reflected not only at health care units, but also in absenteeism. It has been estimated that annually, influenza epidemics are responsible on average for a loss of 1.3 workdays (60), with consequent impact on productivity.

Estimating influenza burden is challenging, as influenza laboratory diagnosis is not usually performed in all suspected cases. As such, the burden of influenza epidemics has been measured through indirect ecologic methods, as time series analysis (10,61). Several of these studies focused on mortality or morbidity due to pneumonia and influenza (P&I) (62–65).

However, using P&I as the outcome may underestimate the impact of influenza on human health and thus on health service needs. Some studies suggest that such indicators may not be accurately reported and, therefore, do not actually reflect the total burden. Schanzer et al. (66) estimated that, on average, only 8% of the excess deaths associated to this virus had influenza reported as the cause of death. Similarly, Baltussen et al. (67) found that of the total excess hospitalizations associated to this respiratory infection, only 12% had influenza as main diagnosis. These results, and the fact that other chronic diseases are risk factors for severe influenza complications, have substantiated the analysis of influenza impacts on chronic obstructive pulmonary disease and other respiratory illnesses, diabetes, ischemic heart disease, cerebrovascular diseases among others causes of death or hospitalizations (68–70).

For the estimation of influenza associated excess (burden), studies have employed indirect ecologic methods using the Serfling approach (71) and regression models using Poisson, negative binomial regression and autoregressive integrated moving average (ARIMA) models to estimate influenza associated excess mortality or hospitalizations rates (6,72–75). There are two main approaches in estimating influenza-associated excesses. One is based on statistical models that include influenza activity indicators as explanatory covariates. Another approach is characterized by not considering covariates and by excluding from the estimating process all parts of the outcome time series where there is evidence of occurrence of some event that might influence the outcome (75).

There are pro and cons in both approaches. Using models with covariates allows estimating influenza associated outcomes by type and subtype of virus, but requires robust epidemiological and virological data (76). In the alternative approach, this specific data requirement is not needed, provided that consistent mortality or

hospitalization time series are available (76). The identification of influenza epidemics in the time series analysis requires influenza surveillance data with information on influenza virus type and influenza epidemic activity period and other factors like temperature, humidity and other respiratory virus (70,77).

Also, and when available, the identification of other events that contribute to mortality or hospitalizations distribution, like secular trend or seasonality is desirable so to better fit the model to the time series and this way improve the quality and the validity of the influenza attributable excess estimate (78).

All the above considered, a worldwide effort to measure influenza burden revealed that, on average, an excess respiratory mortality of 0.6-44.1/100,000 for persons 65-74 years and 1.0-211.8/100,000 for persons  $\geq 75$  years can be associated to seasonal influenza epidemics (4). A similar approach in Europe, for the 2013-2016 seasons, estimated an average of 30-185 excess deaths per 100,000 inhabitants with  $\geq 65$  years (79). In the USA, an economic cost analysis was associated to the disease burden and revealed that in 2015, influenza contributed to 64.7% of the total annual economic burden of vaccine-preventable diseases (80).

In Portugal, influenza burden has been estimated to be associated with an average of 24.7 excess deaths per 100,000 inhabitants (6) and 19.4/100 000 inhabitants excess hospitalizations due to pneumonia and influenza (1).

Given the well-established risk of influenza for public health, it is important to prevent and/or minimize influenza burden. As with several infectious diseases, it is key to prevent influenza transmission, using community based strategies to prevent the infection and its propagation.

During the 2009 H1N1 pandemic, the European Center for Disease Prevention and Control (ECDC) elaborated a guide to public health measures to reduce the potential impact of influenza. In this document, several pharmacologic and non-pharmacologic measures were pointed out. Non-pharmacologic include several measures that could go from reduce risk of transmission (e.g. confinement, face masks), increase social distance (e.g. schools closure, home working) to disinfection measures (e.g. hand washing) (81). Their efficacy facing seasonal or pandemic influenza differ. Namely, the combined use of hands hygiene and facemasks have demonstrated to have a modest efficacy of 27% against influenza (82), but the use of facemasks still needs to be further implemented at community level (83).

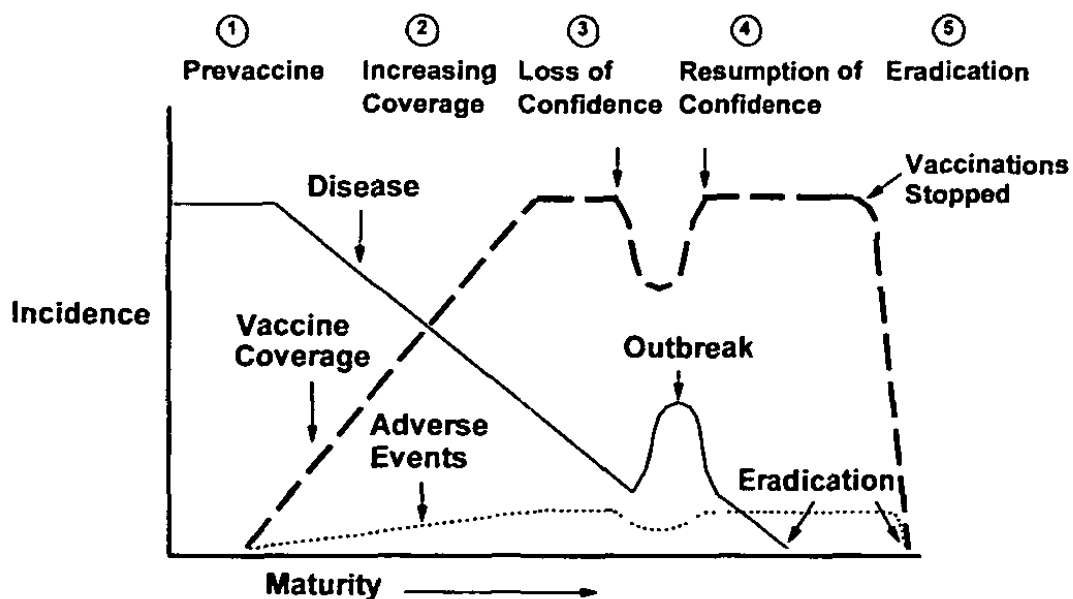
The pharmacologic measures includes, among others, antivirals and vaccines. The first has been used as an individual approach and the vaccine as a community based one.

Given the modest efficacy at community level of non-pharmacologic measures, influenza vaccination continues to be the keystone of primary prevention of influenza virus infections, for both seasonal and pandemic virus.

## 2.2 Influenza vaccines and vaccination strategies

Vaccines are one of the main public health interventions, responsible for reducing the incidence of several infectious diseases and their related morbidity and mortality (84). The discovery of vaccines against pertussis, measles, diphtheria, tetanus has been considered as a changing point in the worldwide mortality time series and in the increment of life expectancy (85). The implementation of vaccination programs led to the decline of infant mortality and also avoided complications of these infectious diseases, especially in young children, allowing them to achieve their full potential free from infectious diseases-related sequelae (86). The success of vaccines was so considerable that, for a set of infectious diseases, the designation of vaccine preventable diseases (VPD) is often applied.

Immunizations programs evolutes towards the increase of vaccine coverage and decrease/ eradication of the disease (Figure 2).



**FIGURE 2. EVOLUTION OF IMMUNIZATION PROGRAMS (18)**

Since the 1950's an egg propagated vaccine against influenza is available (8). Influenza vaccination has been considered as one of the main public health measure for influenza control, with a recognized role in reducing the risk of developing the disease but mainly to the occurrence of their complications (9).

Influenza vaccines could differ in i) the number of strains included in the formulation, ii) the type of vaccine and iii) manufacturing process. Accordingly, vaccines could be trivalent (contains one B virus lineage, one AH1 and one AH3) or quadrivalent (containing the two A subtype and the two B lineages) (8); inactivated, live attenuated (87) and with adjuvanted or not (88). The most common process to obtain vaccines is through egg propagation (89), but the use of cell culture or plants has become more frequent (90).

Due to the virus high capacity to acquire new mutations that allow it to escape the human immunologic system (virus drift), the vaccine formulation changes every year. Also, the immunity conferred by the vaccine has been described has not longstanding (4 to 8 months) (91), meaning that even if the vaccine was not reformulated, a yearly boost would be necessary. Hence, the influenza vaccination strategy is considerable different from other VPD and respective immunization programs evolution.

Taking in consideration the WHO “The Global Action Plan for Influenza Vaccines” (92), most countries have an influenza vaccination strategy or program. There are several factors to be taken into account when designing an influenza strategy (10):

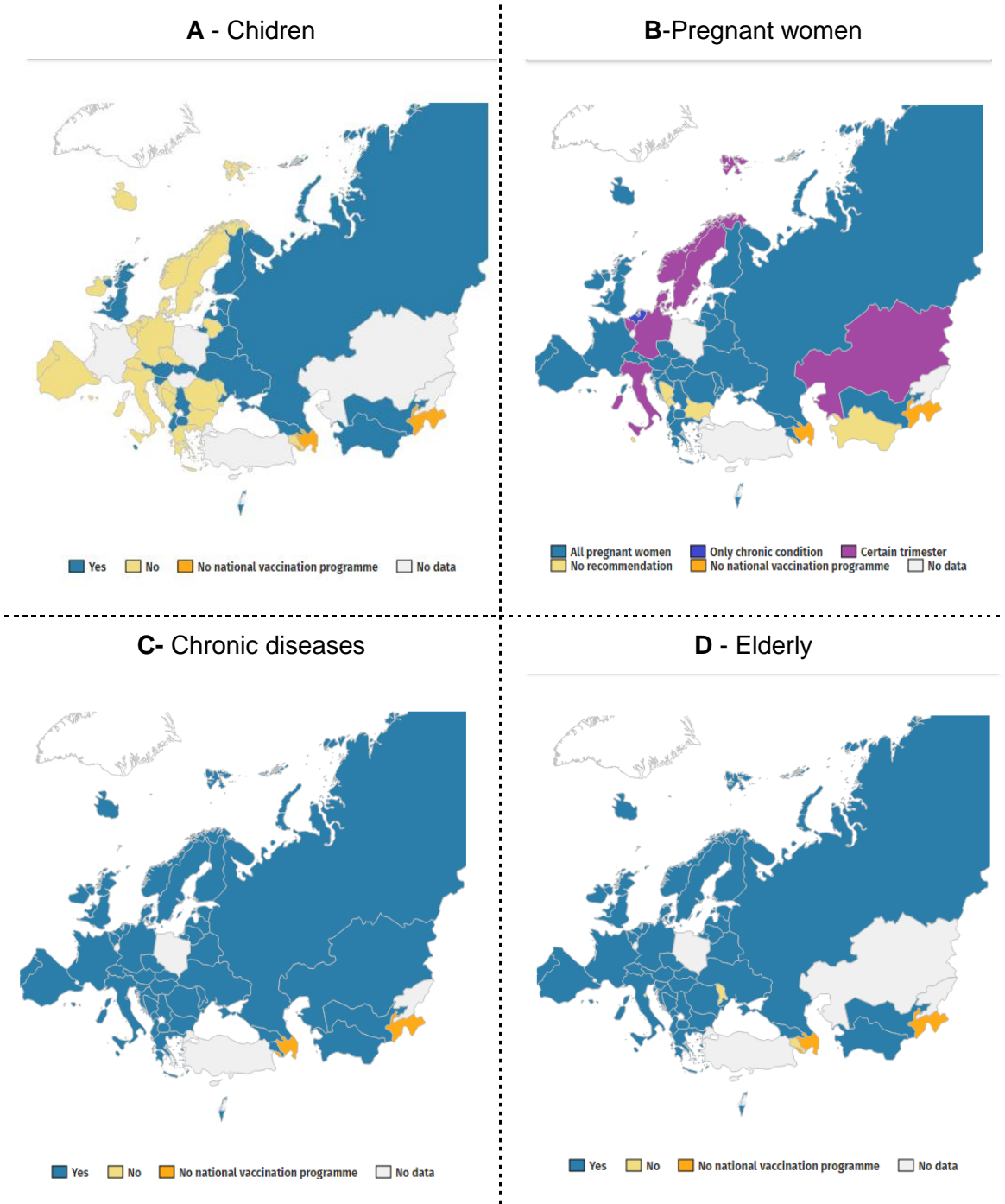
- The ambit : universal, all the population eligible for the vaccine uptake, or targeted to specific groups (based either on age or a risk approach);
- The target groups: according to age (children and older adults with 65 and more years); exposure risk (health professionals); clinical risk (pregnant, people with chronic condition)
- The type of the vaccine (trivalent, quadrivalent, adjuvanted, high-dose)

The combination of these factors conduct to different strategies applied all over the world. For instance, the USA, Canada (93) and Australia recommend universal vaccine, while other countries target individuals with high-risk for influenza complications. In the tropical and sub-tropical areas, different strategies are adopted, ranging from no influenza vaccine program to programs that target children or older adults (with different age cut-offs being applied) (94).

In Europe, the targeted influenza vaccination strategy was adopted by the majority of the countries. A survey conducted in 2010/11 by the VENICE project that included 29 countries in the European Union (EU) and Economic Area (EEA), revealed that influenza vaccine was recommended to all adults in two countries (Austria and Estonia) (95). For the remain 27 countries specific groups of adults were recommended for the annual vaccine uptake (95,96). In 2006/7 season, the older adults (65 and more years) and adults with chronic conditions were included in the vaccination against influenza in



all 29 countries. The list of chronic conditions differed between countries, but pulmonary and cardiovascular chronic diseases were referred by all countries (97). According to information on the European Health Information Gateway (98), in 2015, almost all WHO- Europe region had an influenza vaccination recommendation targeting the older adults (aged 65 and more years) and/or individuals with chronic conditions (Figure 3).



**FIGURE 3. MAPP OF INFLUENZA VACCINATION RECOMMENDATION IN EUROPE: A) CHILDREN, B) PREGNANT WOMEN, C) CHRONIC DISEASES AND D) ELDERLY. SOURCE: EUROPEAN HEALTH INFORMATION GATEWAY (98)**

The strategies adopted by each country are updated towards highest public health impact. In the UK this was the rationale for a phased introduction of a live attenuated vaccine in the pediatric population (with 2 to 16 years) intending the reduction of influenza transmission and maximizing the vaccine effectiveness (99). In order to monitor the immunization program success it is important to monitor some key components of the program, namely, the coverage, effectiveness and impact of the program.

In several European countries the influenza vaccination strategy has relied in recommending the vaccine to high-risk individuals that are more prone to post-influenza complications, namely the older adults (65 and more years), individuals with chronic conditions, children and pregnant women. The Portuguese strategy has been in line with the previous.

Since the 1998/99 season the Portuguese official recommendations have been including the older adults (65 and more years) and some chronic conditions. The list of conditions for which the influenza vaccine is recommended increased and includes nowadays chronic respiratory, cardiovascular, renal, kidney, immunocompromised and neuromuscular diseases (19,100).

In the 2017/18 season, influenza vaccination was recommended to the older adults (65 and more years), individuals with more than 6 months and with a chronic condition, pregnant, and caregivers of children with less than 6 months with a chronic condition (11). Health professionals were also targeted for the annual influenza vaccine uptake.

Up to season 2017/18, the available vaccines were trivalent inactivated. In order to promote the vaccine uptake in the older adults, the IV is offered free of charge, since 2012, to all individuals with more than 65 years of age. The implementation of the Portuguese IV strategy has been measured through the estimation of the vaccine coverage overall and in specific groups (14).

### 2.3 Influenza vaccine coverage

Measuring the vaccine coverage, i.e., the proportion of vaccinated individuals in a given population, is a first step in the assessment of any vaccination strategy. It allows to capture how and where and how many individuals are taking the vaccine. A successful vaccination campaign would attain established coverage targets in terms of

population and coverage – indicating the country's preparedness in relation to influenza prevention plans (14).

Taking in consideration the potential benefits, that these high-risk individuals may gain by annual vaccination, in 2003 the World Health Organization established a 75% target of vaccine coverage to be attained in 2010 (101). In 2009 this motion was reaffirmed in a European Council recommendation to reach 75% vaccination coverage in the high-risk group by 2015 (22). However, the published results on influenza vaccine coverage, indicate that the target is far from being achieved in the majority of European countries.

A survey conducted in 11 countries in Europe in the 2004/05 season on vaccine coverage in high-risk group revealed great disparity. The Netherlands had the highest vaccine coverage, with more than 75% of the high risk group being vaccinated, and Greece had the lowest (<27%) (102). Countries as Austria, Belgium, Denmark, France, Germany, Italy, The Netherlands, Spain, Sweden and Switzerland varied in the coverage value and in the group that reached higher coverage rates (102).

In the 2014/15 season, however, the influenza vaccine coverage scenario changed (103). Considering older adults with 65 years and more, only Scotland reached the 75% target and in the Netherlands the vaccine coverage dropped to below 70% (103). For individuals with chronic conditions, the coverage in most countries was below 40% (103).

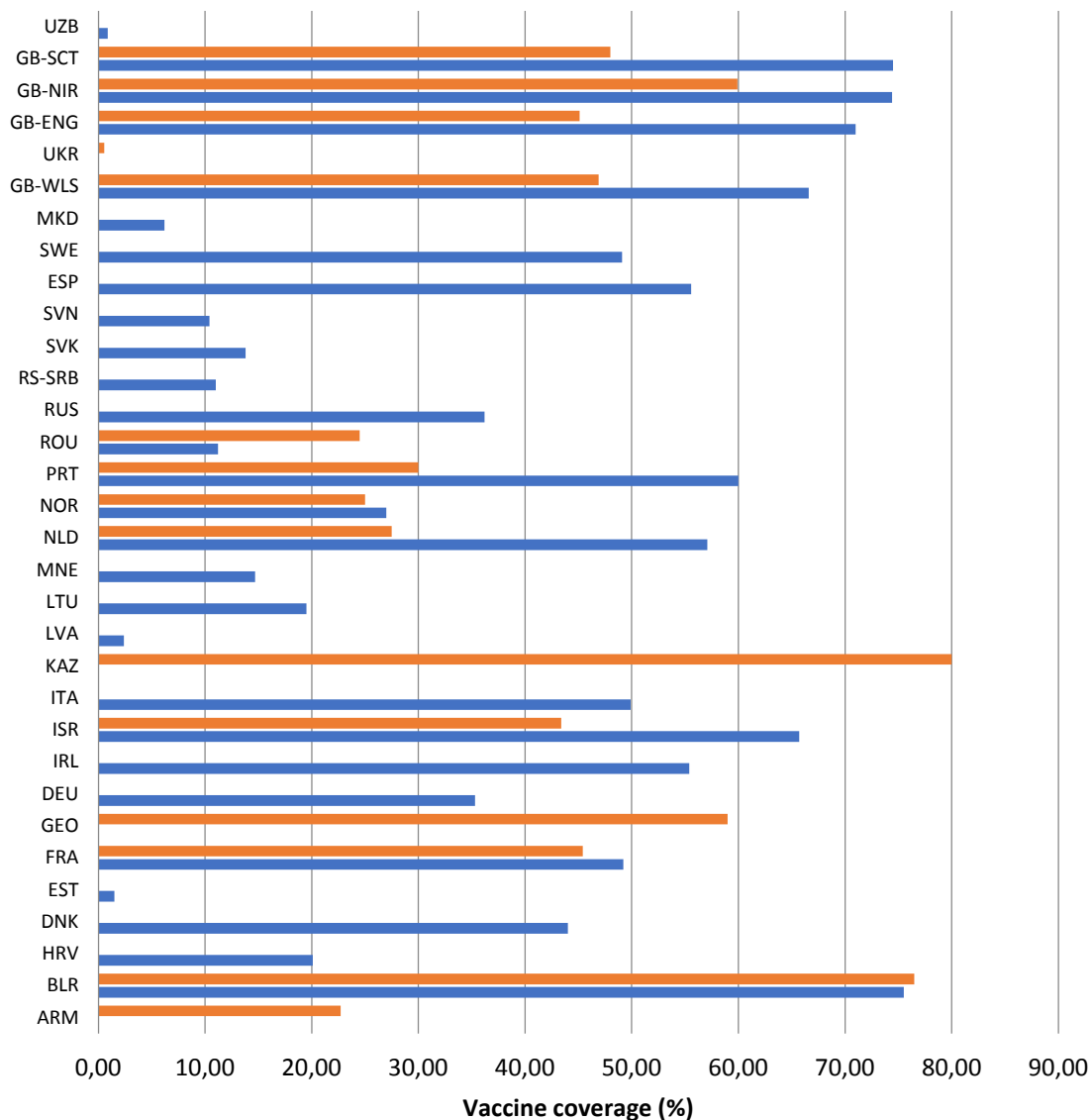
In the 2015/16 season, in the WHO-European region, the IV coverage was systematically higher in the older adults (65 and more years) than in individuals with chronic conditions (Figure 4), and only Byelorussia accomplished the 75% coverage target for both risk-groups (98).

According to a European estimation of the health and economic benefits of the seasonal influenza vaccination conducted by Preaud et al. (32) in 2014, only 44% of the eligible population (including high-risk and health care workers) was taking the vaccine annually and none of the EU 27 countries reached the WHO target of 75%.

In Portugal, a more conservative target of 60% was settled for the older adults (65 and more years) population, and this was expected to be achieved by season 2014/15 (104). The community-dwelling based vaccine coverage (VC) monitoring system, that has been in place since 1998, indicate that the VC, within older adults, was approximately 50% during post-pandemic period (19,100) and increased into 60% in the 2017/18 season (20).

IV coverage is considerably lower in the group with chronic conditions (about 30% in post-pandemic period, increasing into approximately 40% in seasons 2017/18 season).

In summary, in both high-risk groups, the 75% VC target is still far from being achieved. Finding factors associated to vaccine uptake is of extreme importance to accomplish the proposed target of the vaccination strategy.



\*Countries with no column - Data not available

**FIGURE 4. INFLUENZA VACCINE COVERAGE IN THE WHO-EUROPEAN REGION IN THE 2015/16 SEASON**

### 2.3.1 Factors associated with IV uptake

Several authors have studied factors associated to the IV uptake, with the intention of determining the main predictors of the vaccine uptake and thus contribute to the vaccine strategy success. This increased research on IV uptake and associated

determinants allowed systematic reviews and meta-analysis to be conducted. Some focused in the social determinants. A review published in 2007 (105) on the determinants of influenza and pneumococcal vaccine observed that higher age and presence of chronic condition were strong positive predictors of IV uptake. Other predictors identified in the articles reviewed were, higher education, recommendation from the doctor or family or media, self-reported poor health, larger household (>3 elements), low income, number of visits to the general practitioner (GP), marital status, IV uptake in previous seasons, preventive care (screened for cancer) and gender. On the other hand, lack of recommendation and no risk perception were the factors associated to low IV uptake.

A review published in 2013 (106), focused only on the social determinants of seasonal influenza vaccination of older adults population (65 and more years), review comprised not only quantitative but also qualitative studies. Concerning personal characteristics, the authors described gender, age, marital status, education, race, socioeconomic status, presence of chronic condition, cultural values and beliefs. On the patient behavioural dimension, the authors listed the following: prior experiences of influenza or vaccination, concern about the vaccine, perceived risk or susceptibility, perceived or self-appraisal health status. Finally, broader contextual factors were identified, namely, the health system, accessibility of IV, affordability and visits to a health care unit. Personal characteristics, patient behavioural and contextual factors were positively or negatively associated to IV uptake depending on countries.

Jain et al. (2017) (107), conducted a systematic review that targeted individuals with 60 and more years and the social determinants of IV (and other vaccines, such as pneumococcal and zoster) coverage. Concerning IV, the results indicate that living alone, marital status, urban/ rural area residence, country of birth (different from the residency) were social determinants and all (except for birth country different from residency) increased IV uptake. For remain factors, such as education, income (household or individual), socioeconomic level and social class, no consistent association was observed.

Other authors reviewed the personal beliefs and attitudes towards the vaccine. In 2016 a review was published fully dedicated to barriers of IV uptake intention and behaviour. They analysed this using the Theory of Planned Behaviour (108). Barriers of IV uptake were lack of confidence, inconvenience, calculation and complacency.

As many robust evidence may derive from systematic reviews, the country specific context may only be studied in country specific research. This was the case for China

(109), Taiwan (110), Poland (111), France (112,113), USA (114), Italy (115), Germany (116,117) and Spain (118,119). The majority are focused only in the adults aged 65 and more years but some include other high-risk individuals (Table 1). The country specific studies results evidence that factors that are associated to IV uptake differ between countries and target of the study. For the majority of countries age is a relevant and significant factor that is associated to IV uptake (Table 1).

**TABLE 1 SUMMARY IV UPTAKE STATISTICAL SIGNIFICANT ASSOCIATED FACTORS (COUNTRY-SPECIFIC ODD- RATIO OR POINT ESTIMATES)**

Country	China	Spain	Germany	Taiwan	Germany	Poland	France	France	Italy	Spain
Study target population	All age	High-risk	High-risk	Older adults	Older adults	Older adults	All ages	All ages	Adults with COPD	Older adults
Ref.	(109)	(119)	(116)	(110)	(117)	(111)	(113)	(112)	(115)	(118)
Sex		1.15								
Age	3.3	2.88	6.55	7.72		7.69	0.8	23.15	1.42	2.37
Education	1.6							3.32	0.61	
Urbanization						7.69	1.6			1.36
Income								0.54		
Nationality		0.59	1.23							
Health conditions	1.9	1.94	1.37	1.31		2.7				1.58
Self-health status			0.72						0.67	1.24
Health care worker (HCW) recommendation	5.4		3.05		3.1					
Target group							4.0			
Smoking			0.91	0.67					0.65	1.64
Physical activity				1.43						
Family recommendation					19.8	3.57				
IV benefit	1.3				23					
IV side effects	0.6		1.16							
Awareness IV free	1.9					5.0				

Several studies are multi-country comparisons and aimed not only to estimate the vaccine coverage but also to investigate determinants that promote the IV uptake. In 2007, Muller and Szucs (120) conducted a telephone survey in Germany, Italy, Spain, France and UK for 3 consecutive seasons. The objective was not only to estimate the IVC but also, to i) search for associations between VC and demographic parameters and ii) determinants of being vaccinated and people's beliefs towards the vaccine. Results indicate that age, having a chronic condition were positively associated to the vaccine uptake. Gender, on the opposite was not associated to IV. On the beliefs dimension, the influenza severity, a HCW recommendation and not wanting to infect family/ friends were associated to IV uptake. In 2009, the same author published a study that combines the information collected in 11 EU countries (121) (France, Germany, Italy, UK, Spain, Austria, Czech Republic, Ireland, Poland and Portugal) aimed at analysing socioeconomic factors of IV for 7 consecutive seasons. For Portugal, the results indicate that being male, size of the household (3 or more individuals decrease the IV uptake), living in a site larger than 50000 residents) was positively associated to IV uptake. No effect was observed for income or education.

In another study conducted in the mainland Portuguese population in 2013, Santos et al. (15) intended to understand the potential reasons for high-risk group individuals not taking the influenza vaccine. Lack of awareness of the risk for complications and fear of adverse vaccine effects were the main reasons for not looking for immunization.

Several strategies have been used along Europe to promote the vaccination among the older adults population (65 and more years) (14). This included, besides having recommendations to target groups, having financial incentive or career objectives to the health care workers; implement awareness campaigns in different settings; personal letter from a health professional and reimbursement or free vaccine. In Portugal, besides media and internet vaccine promoting campaigns, specific measures to increase the immunization acceptance have been implemented (14). This included offering the vaccine free of charge, since 2012, for the older adults (65 and more years), reduction of the vaccine price for individuals with some chronic conditions and the possibility of taking the vaccine in both health centre units and pharmacies.

### 2.3.2 Factors associated with repeated IV uptake

The described influenza vaccine uptake determinants research, however, only reflects one aspect of the influenza vaccination, i.e., what are the factors associated to vaccine uptake in a given season. According to the IV recommendations, in regards to influenza, an adequate preventive care against influenza requires high levels of

influenza vaccine uptake every year. Therefore, it is important not only to estimate the IV coverage in a season, but also the proportion of individuals that take the vaccine in a yearly basis, i.e., are repeatedly vaccinated.

Studies on the regular vaccine uptake are scarcer and focused in specific diseases/age groups. For instance, in a study conducted in Taiwan (122), the authors had the objective of identifying determinants of repeated IV uptake in the elderly population. Besides sociodemographic factors (predisposing factors), the authors took in consideration enabling factors (work, household income, urban/rural area, social support, difficulty in activities of daily living (ADL) and instrumental activities of daily living (IADL), need factors (self-assessed health, number chronic conditions, outpatients visits and hospitalizations); health behaviour factors (medical seeking behaviour, smoking, drinking, exercise, use preventive health examination). Results indicate that being 70-74 years, living in rural area, having chronic condition, outpatient visits, and having preventive health examinations were positively associated to regular IV uptake. Having ADL difficulties and use of alternative medicines were less likely to undergo for IV uptake.

In a study conducted in the USA, Quinn et al. analysed the predictors of influenza vaccination in the high-risk adults across five seasons (114). Main results indicate that approximately 47% of the surveyed population took the IV on a yearly basis.

### 2.3.3 Approaches to study IV uptake and vaccine coverage

For the adoption of healthy preventive measures, the mere existence of positive environment and policies is not sufficient. As stressed out in the Ottawa Charter for Health Promotion (123), health promotion is a comprehensive, multi-strategy approach, that incorporates both external environmental factors but also individual motivation and education.

In relation to influenza vaccination, Blank et al. (14), found that rather than a specific single strategy, a combination of policies and strategies increases the vaccination coverage. This result emphasis that IV uptake is a multidimensional issue that needs a multifactorial approach. Different conceptual frameworks can be adopted to tackle the previous. The ecological models are one of them and are based in four key pillar : *(1) there are multiple levels of influence on specific health behaviors; (2) influences on behaviors interact across these different levels; (3) ecological models should be behavior-specific; and (4) multi-level interventions should be most effective in changing behavior* (124).



According to Sallis et al. (124), these models can be used to develop comprehensive intervention approaches that systematically target mechanisms of change at each level of influence. The limitation of them, is the lack of specificity of the models and thus the need to identify critical factors in each behavioral problem (124). Table 2 adapted from Sallis et al.(124), summarizes the ecologic models used to guide interventions.

In Portugal, the proportion of individuals in the high-risk group that take the IV repeatedly on a yearly basis is unknown. Also, is still unclear if the factors associated to IV uptake in a given season are the same that predict the repeated immunization. Thus, identifying factors related to repeated IV uptake would be important for developing effective strategies to overcome barriers to vaccination.

From the summary table it is evident that among social ecologic models for interventions only the social ecologic model, with five levels, was used for research on influenza vaccines. Moreover, it was used for pandemic vaccine and no study was found for seasonal influenza vaccine.

**TABLE 2. SUMMARY OF ECOLOGIC MODELS MAIN FEATURES USED FOR INTERVENTIONS  
(ADAPTED FROM SALLIS ET AL. (124))**

<b>Model</b>	<b>Author (year)</b>	<b>Features</b>	<b>Used influenza vaccine research</b>	<b>in</b>
Operant Learning Theory	B. Skinner (1953)	F. Based on the premises that environment has direct effect on behaviour		
Social Learning and Social Cognitive Theories	Albert Bandura (1986)	Environmental (mainly social environment) and personal influences behavior. Does not account for physical, community, or organizational environments		
Ecological Model of Health Behavior	Kenneth McLeroy (1988)	Five sources of influence on health behaviors: intrapersonal factors, interpersonal processes, institutional factors, community factors, and public policy.		
Social Ecology Model for Health Promotion	Daniel Stokols (1992, 2003)	Based on the four assumptions of social ecologic models	Determinants of pandemic vaccine uptake (125,126)	
Structural-Ecological Model	Deborah Cohen and others (2000)	Four categories of structural influences: (1) availability of protective/harmful consumer products, (2) physical structures, (3) social structures and policies, and (4) media and cultural messages.		
Theory of Triadic Influence	Brian Flay and J. Petraitis (1994)	Main factor that affect all behaviour are genes and environment , three streams of influence on behavior are intrapersonal, social, and sociocultural.		
Model of Community Food Environments	Karen Glanz and others (2005)	Focused on eating behaviors		
Resources and Skills for Self-Management Model	Edwin Fisher and others (2005)	Based on integration of individuals' skills and choices with support they receive from the social environment, as well as physical and policy environments of communities		

## 2.4 Influenza vaccine effectiveness

The second component to be addressed within the vaccination strategy is the vaccine capacity to reduce the risk of disease, measured in real field condition, i.e., the vaccine effectiveness.

In general, the vaccine effectiveness is calculated from the Greenwood and Yule formula (cited in (127)), and represents the reduction of risk of disease in the vaccinated when compared to unvaccinated:

$$VE = \frac{ARNV - ARV}{ARNV} \times 100$$

Where

VE: vaccine effectiveness

ARNV: attack rate in the not vaccinated and

ARV: attack rate in the vaccinated

The knowledge of the disease reduction due to influenza immunization is of extreme importance for accessing the benefits of the vaccine uptake. Within season, influenza vaccine effectiveness (IVE) estimates permits to implement alternative measures when the protection conferred by the vaccine is low. Monitoring IVE on a yearly basis allows evaluating the vaccine on longer terms.

Given the yearly reformulation of the vaccine, IVE protection may vary from one season to another. This is related to the match between circulating virus and the ones in the vaccine composition. As such, an annual effort has to be taken in order to evaluate the protection capacity of the influenza vaccine every season. This has been the challenge that several networks have accepted, in order to present annual IVE estimates for their country or region (24,50,128–130). Data has been collected specifically for the IVE studies (130–132), or alternatively using clinical registers and laboratory data collected by the influenza surveillance systems (129,133,134).

### 2.4.1 Influenza vaccine effectiveness and influencing factors

Several factors have been found to influence IVE, some related to the vaccine (28,87,135,136), others with the circulating virus type and sub-type (137–141). Finally there are a number of individual characteristics and health behaviors that should be considered when evaluating the association between influenza vaccine and influenza infection such as sociodemographic, health status, previous vaccination/ exposure to infection and tobacco consumption (142–148).

In order to dissect the enumerable factors that may influence IVE, it is important to understand the natural immune response to influenza infection. The role of

hemagglutinin (H) and neuraminidase (N) viral protein in the virus infection and propagation is crucial in the host immune response. The H is responsible for binding in the host cell and allow the entrance of the virus, while N is responsible for replication and spread into other cells and hostess (149). As such, the primary mediator of protection is producing antibodies able to neutralize the H and thus the viral infection.

Measuring the titers of H specific antibodies allows assessing the host protection against specific strains of influenza. The measurement is done using antigenic analysis, specifically essays of H inhibition (HI). The immune response to influenza also triggers other viral protein (N and M) antibodies, however their specific role in the immune response is unclear and also, the methods to measure these antibodies are technically challenging (87). In the natural response to influenza infection, other cells take important role, namely the T cells, CD4+, CD8+ and B cells (87). While the natural exposure to influenza triggers this complex immune response that could result in both strain specific but also broader immunity, the vaccine mainly induces mainly strain specific immunity (150).

As referred, the vaccine strain composition is decided 6 months previous to the start of influenza season, and the selection is based on the premises that will match the circulating virus. Given the specific strain immunity conferred by the vaccine, it is crucial to obtain high correspondence between the vaccine strain and the circulating virus. An HI antigenic distance of 2 fold, corresponds to a sub-optimal match, and a possible reduced vaccine effectiveness (151).

Not only antigenic information is important in the IVE equation, but also the information on genetically drifted virus. IVE studies have increasingly include genetic characteristics of the circulating virus (26,152–156). The unmatched vaccine strain and circulating virus were the reason for lower IVE in 2004/05 and 2005/06 seasons in USA (157) and in the northern hemisphere in the 2014/15, where a drifted A(H3N2) virus strain circulated (158–160). In a 8 season analysis, specific for B virus and respective lineages, Skowronski et al.(161) found that trivalent inactivated vaccine conferred at least 50% effectiveness regardless of the B lineage present in the vaccine. This result could be explained by some cross lineage protection (162). Besides match between circulating virus and vaccine composition, IVE results have been reported to be lower against A(H3N2) virus compared to A(H1N1) or B virus, either considering outpatient (140,163) or inpatient (141) influenza outcome.

The vaccine induced immune response has been described as not longstanding (4 to 8 months) (91), and there are several reports of intra-season decay of protective

antibodies, a phenomenon called waning immunity (91). In single season analysis, Belongia et al. (164) reported a time decreasing IVE after vaccination for the 2007/18 A(H3N2) dominated seasons and similar results were described by Pebody et al. in the 2011/12 late A(H3N2) season (165). Multiple seasons analysis also described this potential waning vaccine protection. Ferdinands et al. (166) reported a time decreasing IVE in the US IVE network in seasons 2011-12 to 2014-15 for all the virus type/subtype. Kissling et al. (136), within the European I-MOVE network, described for the 2010/11 to 2014/15 seasons the same type/subtype waning effect, but results revealed a faster time decay for IVE against A(H3N2).

The vaccine type has also been described as inducing different magnitude of individual's immune responses. The inactivated vaccine produces a higher H specific response than LAIV (87). On the other hand, LAIV produces higher CD4 T cell response than inactivated vaccine (87). Systematic review and meta-analysis on adjuvant vaccine for the older adult population estimated an IVE of 51% (95% CI: 39–61%) against hospitalizations for pneumonia & influenza among community-dwelling individuals (167). In the same study, comparing adjuvant with no adjuvant trivalent inactivated vaccine the authors observed that the adjuvant vaccine were more effective in reducing influenza and pneumonia and influenza hospitalizations (167). Also to be considered, is the high-dose vaccines that demonstrated a higher performance in the 65 years and more population when compared to standard-dose (168). Efficacy meta-analysis indicated that patients that took the high-dose vaccine had a relative risk of 0.76 of developing laboratory-confirmed influenza (169).

On the other hand, there are some host specific factors that may compromise the individual ability to produce adequate antibodies after vaccination (148), namely, age and correspondent age-related comorbidities, genetic polymorphism and chronic immunocompromised conditions. The age related decline of the immune function, or immunosenescence (170), may explain the lower influenza vaccine effectiveness in older adults. However, up to date research was not able to find statistical differences of IVE in older adults compared to younger individuals (171).

In addition, there are genetic polymorphisms and sex specific hormonal responses that could contribute to differential immune response. With this potential sex effect modifier as research question, Chamber et al. (172) analyzed the Canada IVE for 7 seasons (from 2010/11 to 2016/17), and results indicate some interaction of sex and IVE, for some virus type and seasons, being the IVE higher for females.

Looking to specific chronic conditions, the reduced immunocompetence of immunosuppressed individuals (for instance under cancer treatment or HIV) (148) or the statins uptake for lowering the cholesterol levels (173), may impair individuals capability to achieve adequate antibodies titers. Another chronic conditions with high risk of influenza complications is diabetes. A systematic review and meta-analysis on patients aged 18-64 years with diabetes, estimated that the influenza vaccine was 58% (IC95%: 6 a 81%) against all hospitalizations and 43% (IC95%: 28 a 54%) for pneumonia and influenza hospitalizations. Once again, authors stated the need for more studies with quality to robust these results (174). Considering all individuals in the high-risk group, a qualitative systematic review conducted by Restivo et al. (175) reported IVE of 51.3% (IC95%: 40.7 to 60.1) for the 2014/15 season and of 53% (IC95%: 4 to 77) for the 2010/11 in Spain.

For all the previous described host specific factors (age, chronic condition, sex), IVE may be lower even in a well match season (148).

Finally, there are some factors related to previous vaccination or natural infection that need to be addressed in this IVE associated factors review. The relevance of such studies are related to the vaccination premises that recommend the yearly influenza vaccination. The rationale for the influence of past influenza uptake in current season influenza effectiveness goes back to the immunity acquiring process. Potential explanations for this, negative or positive, interference include the i) original antigenic sin hypothesis (149); ii) residual effect from past vaccination (176) or natural influenza infection (177); iii) antigenic distance hypothesis (178).

The original antigenic sin hypothesis consists in the premises that the first antigenic strain that the individuals encounters in their life, conditions the future immunity (149). Within this theory, future exposure to infection or vaccine do produce specific antibodies, but the antibodies for early exposure strain are increased and maintained in high levels (149).

The phenomenon of antigenic imprinting is related to first influenza virus exposure and the subsequent process that lead to an immunological memory that may shape the future immunity responses (149,179,180). Finally, the antigenic distance hypothesis, is related to the strains included in the vaccine and the circulating virus: this hypothesis predicts negative interference from prior vaccination when the antigenic distance between vaccine and circulating strains is large but the distance between consecutive vaccine components is small (178,181).

Multiple seasons studies results suggest that consecutive vaccination could have a negative effect on current season IVE against A(H3N2) (182,183); on severe hospitalized with A(H1N1)pdm09 confirmation (147) or could have no effect (181,184). Systematic review and meta-analysis results indicate that vaccination in two consecutive seasons were associated to greater protection against influenza A(H1N1) and B when only compared to prior season vaccination (146,185). The difference point-estimate of the IVE reached 25% against A(H1N1) and 18% against B virus (146). Overall, results suggest that several seasons of vaccine uptake were as protective as current season vaccination (186–188).

All these IVE associated factors may have direct impact on the vaccination strategy. Also, given that the influenza vaccine is recommended to older adults (65 years and more) and for individuals with chronic conditions, it is important to continue studies to evaluate how age and medical conditions affect the IVE. By example to evaluate a vaccination strategy that also target young individuals with the objective of reducing population transmission and have a indirect effect of the individuals with chronic diseases our aged 65 and more years. To robust and complement all findings, it is imperative to measure IVE as accurately and unbiased as possible.

The annual estimation of the influenza vaccine effectiveness requires the implementation of specific studies. Seasonal influenza vaccine effectiveness can only be measured using observational studies, using namely the test-negative, cohort or screening method designs.

One of the simplest and quickest approaches to implement is the screening method (189), which consists in comparing the proportion of vaccinated individuals with the outcome under study with the proportion of vaccinated in a comparable population group (18). For its implementation, few resources are needed and as such the estimation of vaccine effectiveness is simple and quick. However for its correct application it is necessary that the coverage of the vaccine in the population is comparable with the population from which the patients with the study outcome came from. Equally crucial is the correspondence between the proportion of cases and population properly and fully vaccinated (127). Screening method is easy to implement (127), can be used within routine surveillance to provide yearly IVE estimates (190), however IVE estimates can be inaccurate if the method assumptions are not fulfill (189).

Cohort design is appropriate when there is a well-defined at-risk population (18). After defining the sampling base and constituting the cohort, the vaccination status is

recorded, and individuals are monitored throughout the season. The estimated vaccine effectiveness is calculated based on the relative risk of disease in the vaccinated group compared to the unvaccinated group (191,192). Cohort studies allow studying other questions such as the effect of previous vaccination but are difficult to implement given the need for laboratory confirmed cases and need to have well defined risk population (193).

The test negative design has been widely used in IVE monitoring studies, since it is easy to implement and minimizes confounding by health seeking behavior (192,194,195). These features combined with a specific outcome such as laboratory confirmed influenza, reassure the assessment of unbiased IVE estimates (144). However, there are issues related to the selection of the negative control that has been discussed (196) and still needs to be further evaluated.

The use of such type of design does not impair the evaluation of other types of bias either selection, information or confounding that could arise from the implementation process. One particular type of bias that can have an important impact in over or under estimation of VE is confounding (29).

Methodologies for selecting relevant covariates have been based either on significance testing or change-in-estimate approaches (197). Consequently, the adjustment variables that can differ every season have been described as related to the virus circulation. However, this difference could be partially attributable to study implementation and not to confounding bias. This data driven approach depends on the power to detect differences and this is highly related to the sample size. On the other side, inclusion in the model of the whole set of covariates regardless their statistical significance in order to control for confounding may lead to large standard errors and biased coefficient estimates (197).

A causal approach, based on a casual model diagram representing causal relationship of variables has been proposed to overcome this problem (198). One class of causal diagrams is the directed acyclic graphs and was used to dissect the bias problem in IVE studies (29,199). Lane et al. (145), proposed a direct acyclic graph for IVE studies so to allow adjustment with a smaller set of variables and reduce over fitting. The set of variables that needed to be accounted for confounding adjustment included age, immunocompromised conditions, time within the season (date of disease onset). According to the authors (145), this method would be of particular importance in small sample size studies.



The EuroEVA (130) study is the Portuguese component of the I-MOVE (Influenza - Monitoring Vaccine Effectiveness) in Europe network (131). In the national study, the sample size varied between 133-400 influenza like-illness for all aged patients. The potential confounders are investigated and included if they changed crude OR estimate in at least 10% after adjustment by the Mantel-Haenszel method. In certain seasons and for some sub-populations this method led to unstable models with low adjustment quality and other sparse data problems. In order to have national IVE estimates, other adjustment approaches need to be investigated and evaluated.

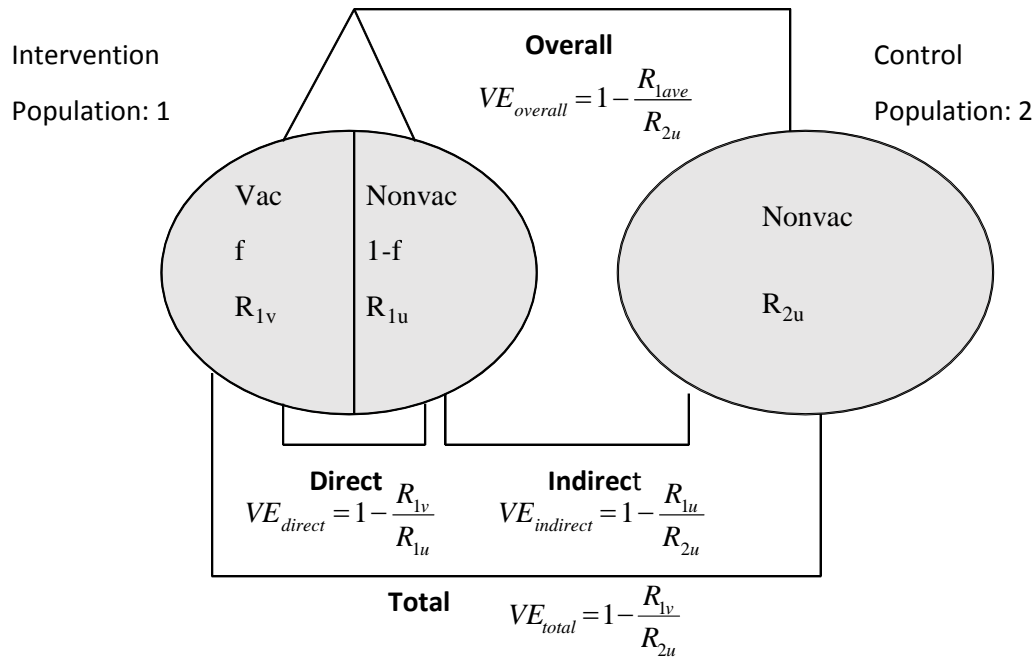
Measuring annual IVE with prospective collection of data is laborious and to obtain estimates with reasonable precision that represents the potential real IVE on population, there is the need to have large datasets, networks or multicentric studies (24,139,200–202).

The use of multicentric studies data requires the design of a common protocol and the implementation of that protocol on a yearly basis. This was the basis of the European network for estimating influenza vaccine effectiveness against medically attended influenza (131). The final objective is pooling the multicentric studies data (144) to obtain a broader and more precise IVE estimates. Such networks are sometimes based in heterogenic settings with different vaccines and recruitment process. Even in networks with implementation of a common protocols (131,203), the inter countries/settings heterogeneity could be an important issue. As such, assessing the study implementation (for its internal and external validity) is needed to robust the study results, its interpretation and use for public health action.

## 2.5 Impact of influenza vaccination strategy

The third axis, is measuring the impact of the vaccination strategy at population level. The vaccination strategy has a broader effect on population, both vaccinated and not (17).

Hanquet et al. (15), based on the previous work of Halloran et al (1991), systematized the vaccine effects (Figure 5).



where  $R$ =rate or risk of disease in vaccinated ( $v$ ) or unvaccinated ( $u$ ); intervention population is a population with a vaccination program, and control population is the population with no vaccination program.

**FIGURE 5. SCHEMATIC REPRESENTATION OF VACCINE EFFECTS REPRESENTED BY HANQUET ET AL. (15)**

According to the schematic Hanquet et al. (15) proposed that different types of vaccine effect occur (Figure 5): direct, indirect, total and overall. The direct effect of vaccine is the result of comparing vaccinated and non-vaccinated individuals, regarding the risk of infection, both groups belonging to the same population where a vaccination program exists (15,17).

The indirect, total and overall effects are measured by comparing intervention population (that includes both vaccinated and not vaccinated individuals) with a control population (with no vaccination program) (17). The indirect effect, is measured through the difference between the disease incidence rate, in the unvaccinated group of the intervention population and the disease incidence rate in a comparable control population without vaccination (17). Also referred to as herd protection (16), the indirect effect captures to what extent the vaccination program reduces the risk of disease for an individual who did not receive the vaccine (17). This indirect effect depends on several factors: vaccine effectiveness, vaccine coverage and reproduction number (16). The reproduction number measures the number of secondary infections: when the prevalence of protected individuals is higher than the herd protection threshold, the

number of secondary cases per infected case is lower than one and this limits the spread of disease. According to Lefebvre et al. , the herd protection threshold for influenza is around 50% to 70%, and depends on both vaccine effectiveness and coverage, among other factors (16). Good level of herd protection is achieved by reducing the potential transmission of the disease with high vaccine effectiveness and/or high vaccine coverage (16).

The total effect is the sum of the direct and the indirect effect of a vaccine in the vaccinated individual under a vaccination program or strategy and is obtained by comparing the incidence rate among the vaccinated group in a population with vaccination program with the incidence rate among the non-vaccinated individuals of the population without a vaccination program.

The overall effect measures the effect of the vaccination program in the entire population, vaccinated and unvaccinated individuals by comparing the incidence rate in the population with a vaccination program against the incidence rate in the population without a vaccination program.

Although no consensual definition exists on impact definition, according to Hanquet et al (15), the impact of the vaccine program corresponds to the overall effect of a given strategy. Accordingly, with the difficulty in finding an impact definition, measuring the impact of a vaccination program is also methodologically challenging. For some infectious diseases, as rotavirus, the impact of vaccination on a given population can be measured by comparing the disease incidence before and after the introduction of the vaccine (15,17). However, for influenza vaccination, with a vaccination strategy in place in majority of countries for a long time, this approach is not feasible.

According to Jit et al. (10), measuring the impact of influenza vaccination program can be achieved in two steps: i) estimate the disease burden and ii) estimate the potential prevented cases. A simple approach in theory, but with several potential errors and assumptions needed to be taken into consideration when interpreting the results (10). This author highlights in particular issues in estimating the influenza burden using specific and sensible case definitions and measuring the vaccine effectiveness.

Infectious disease transmission models, namely, susceptible-infected-recovered (SIR) models, can be used to estimate vaccine effect (204). Within this approach, in each season, a fraction of the population that is susceptible (S) to influenza can become infected (I) and later on recover (R). The transition between stages is obtained by a model, and the model fit depends on quality of epidemiological data. For a set of parameters, several assumptions are made. This kind of approach allows obtaining not

only the direct but also the indirect effect of the vaccination strategy. The downside of this approach is the need to make assumptions and fix some parameters, that are difficult to estimate from representative studies, and that may introduce bias to the results (205,206). Backer et al. (206) implemented this approach and found that for the 2003-2015 period, the influenza vaccine was able to prevent 13% of influenza infection, but more was prevented in more severe outcomes (24% of hospitalizations and 35% of deaths). Weidemann et al. (205) developed such a model for Germany to estimate the impact of the influenza vaccine, of changing the target of vaccination to children. The authors found that the change of vaccination strategy would have considerable benefits to the population (changing from a 8.6% of prevented cases into 17.8%) (205). Statistical modeling approaches have been used in economic evaluation to estimate the vaccination impact (207–209).

A different approach has been proposed to evaluate the existing influenza vaccination strategy and the potential value in vaccinating specific groups of the population (32,210,211). To estimate the strategy impact, they propose to calculate the population prevented fraction (15) (equation 1):

$$\text{Population Prevented Fraction} = (VC \times IVE_{\text{total}}) + ((1 - VC) \times IVE_{\text{indirect}}) \text{ (eq 1)}$$

Assuming that the indirect effect in the high-risk group is residual (due to low VC in other groups of the population) and that the prevented fraction is  $VC \times VE$  (15), the number of averted cases in a season can be calculated using equation 2:

$$\text{Averted} = \text{IRO} \times \frac{(IVE \times VC)}{1 - (VC \times IVE)} \text{ (eq 2) where}$$

IRO – Influenza related outcome (observed)  
IVE – Influenza vaccine effectiveness  
VC – Vaccine coverage

In summary, to measure the IV strategy impact there is the need on information: i) vaccine coverage (VC); ii) on vaccine effectiveness (IVE) and iii) observed influenza related outcomes.

This approach, used by Kostova et al (212), established the method to estimate the number of averted outcomes by the United States of America (USA) vaccination strategy. Jackson et al. (210) observed that for two consecutive seasons, the number of influenza outpatients averted by vaccination varied between 4-41/1000 vaccinated. Alongside with influenza burden, this information was further on included in the Center for Disease Control and Prevention (CDC) influenza page and is regularly updated every season (31). According to the researchers this field of research also highlighted the need for further improvements in the influenza surveillance system (3). The

approach used by the CDC covers several influenza outcomes, with different severity levels. However, not all are available in the end of the season, and for instance, the impact on mortality are only available in the following season. Following similar approach, Preaud et al. (32) estimated that additional number of averted consultations (more than 678 500), hospitalizations (more than 23 800) and deaths (more than 9 800) if 75% of the target group was vaccinated in the European area. Bonmarin et al (33) found that, for older adults in France, in the 2000 to 2009 seasons the vaccination averted 2647 deaths. In the US, Foppa et al (213), also looked into mortality and found that 40 127 deaths were averted by vaccination.

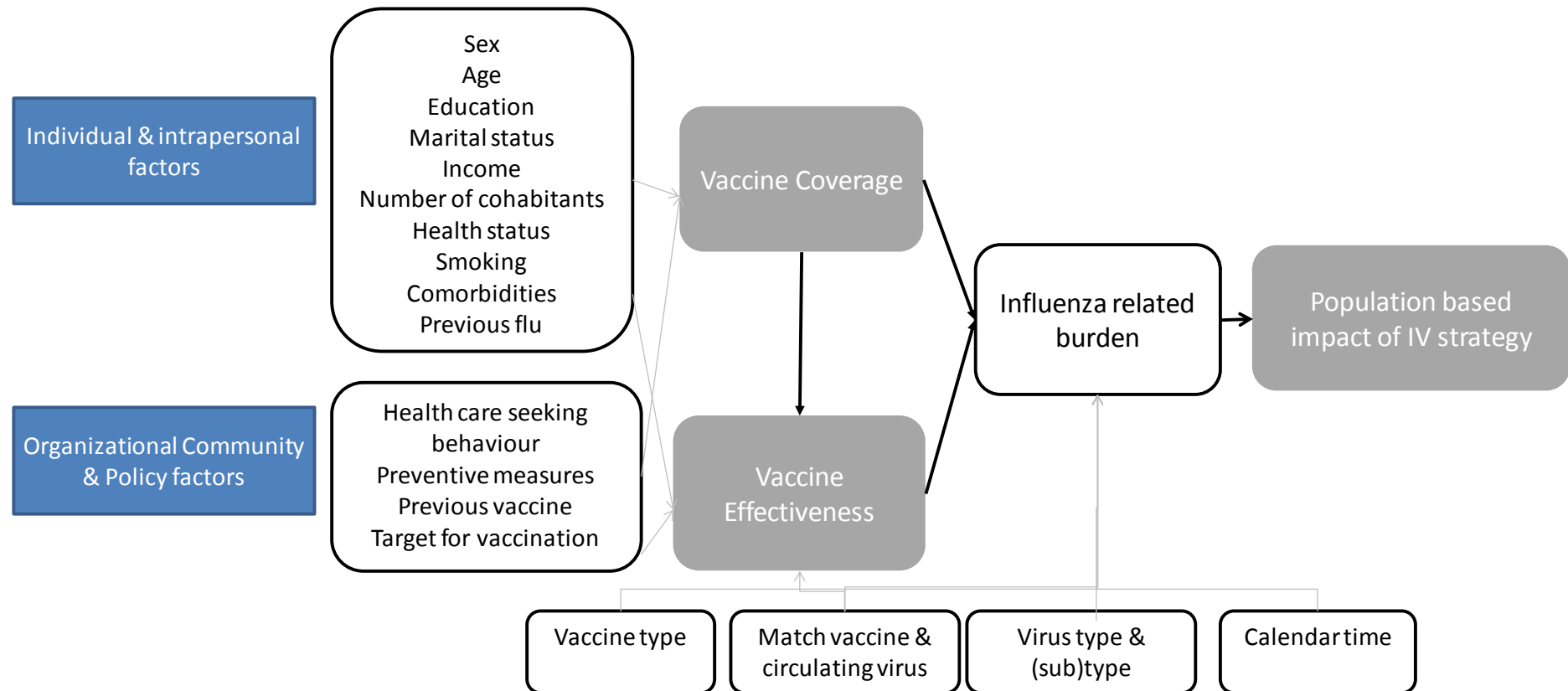
An adapted summary of main impact result is available in table 3. For all this studies, the assumption of no herd immunity was present. This could be a limitation in countries where the vaccine coverage outside the target group is high. In Portugal, besides the study from Preaud et al. (32) that made several assumptions on country specific data, no other study aimed to estimate the impact of influenza vaccination strategy. As such, there is no information on the overall impact of the annual vaccination of high-risk population.

**TABLE 3. SUMMARY RESULTS OF INFLUENZA VACCINATION PROGRAM IMPACT ON MEDICALLY ATTENDED INFLUENZA, HOSPITALIZATIONS AND DEATH**

Season {virus dominated}	Vaccine coverage	Vaccine effectiveness	Number averted events (per 100 000)	Prevented fraction	Country (Ref.)
<b><i>Medically attended influenza</i></b>					
2005/06 - 2010/11	Range: 26.6- 69.6	29.5-43.2	varied from 78.1 to 1450.1	18.4% varied 2.4-21.7	USA (212)
2013/14 {A(H1N1)pdm09}	64.7	39 (0–65)	688.1	20.9%	USA (214)
2014/15 {A(H3N2)/B}	66.0	12% A(H3); 74% B	748.4	7.1 %	USA (215)
2015/16 {A(H1N1)pdm09/ B}	63(62-64)	41 (4 ; 64)	590.6	22.5 %	USA (216)
2016/17 {A(H3N2)/B}	64.8(63.8- 65.8)	20 (-11 ; 43)	686.4	11.5 %	USA (217)
<b><i>Hospitalizations</i></b>					
2005/06 - 2010/11	26.6- 69.6	29.5-43.2	Varied from 2.2 to 53.4	18.4% varied 2.4-21.7	USA (212)
2013/14 {A(H1N1)pdm09}	64.7	39 (0–65)	111.7 (49.0, 203.1)	20.9%	USA (214)
2014/15 {A(H3N2)/B}	66.0	12% A(H3); /74 B	121.5	7.1 %	USA (215)
2015/16 {A(H1N1)pdm09/ B}	63(62-64)	41 (4; 64)	95.8	22.5 %	USA (216)
2016/17 {A(H3N2)/B}	64.8(63.8- 65.8)	20 (-11; 43)	111.5	11.5 %	USA (217)
<b>Deaths</b>					
2005/06-2013/14		29-45		24	USA (213)
2000/09	62%	4.6		21.6	France (33)
2011/12-2012/13	58%	16%	153.3	9.3	Spain (218)

## 2.6 Conceptual model of the thesis

The literature review disclose the interconnection of vaccine coverage, vaccine effectiveness and their impact on the population. Moreover, it evidence the existence of common factors that influence two or more of the components addressed in this thesis. The research conducted was developed in the scope of the following theoretical conceptual model (Figure 3).



**FIGURE 6. CONCEPTUAL MODEL OF THE THESIS**





### 3 Study population, research questions and objectives

The study population encompasses individuals at risk of developing severe complication due to influenza infection, specifically older adults with  $\geq 65$  years and individuals with  $\geq 6$  months with chronic conditions for which the vaccine is recommended. For this subgroup of the target Portuguese national influenza vaccination strategy this study intends at answering the questions:

*"What is the influenza vaccine coverage in the high-risk population, on a given seasons?"*;

*"What are the factors associated with influenza vaccine uptake in one season and continuously over several seasons?"*

*"What is the vaccine effectiveness in reducing the influenza disease and its related complications?"*

*"What is the population impact of the IV strategy?"*

Considering this, the following three main objectives were established:

1. To estimate the influenza vaccine coverage in a season and repeatedly vaccinated over consecutive seasons
  - 1.1. Identify main determinants of influenza vaccine uptake
  - 1.2. Identify the factors associated with repeated influenza vaccination
2. To estimate the influenza vaccine effectiveness in reducing
  - 2.1. Primary care attended influenza and investigate age and chronic condition as potential vaccine effect modifiers
  - 2.2. Influenza hospitalizations
3. To estimate the influenza vaccine strategy impact
  - 3.1. Number of events (primary care medically attended, hospitalizations and deaths) associated with influenza averted by the influenza vaccine strategy and respective preventive fraction



## 4 Methods

To achieve the established objectives, different study designs, datasets and statistical approaches were used. This methods section is organized according to each of the three main influenza vaccination components that are under study: vaccine coverage, vaccine effectiveness and impact of vaccination strategy.

### 4.1 Influenza vaccine coverage and associated factors

Within objective 1, two studies were developed to answer the specific objectives 1.1- determinants of influenza uptake (**study 1**) and 1.2- coverage and factors associated with repeated vaccination (**study 2**). Study 1 aimed at finding determinants of the influenza uptake, using the 5 levels social ecologic model (SEM) as framework (125,219), while study 2 aimed at estimating repeated vaccination coverage over four consecutive seasons and respective associated factors.

#### 4.1.1 Study design

For both studies, secondary analysis of cross-sectional data were performed. Namely, the 5<sup>th</sup> National Health Survey-INS2014, (**study 1**) and the 1<sup>st</sup> National Health Examination Survey-INSEF2015 (**study 2**). The use of two national surveys is justified by the study population (see sampling section) and questionnaire (see data collection section). Detailed information on surveys design and procedures was published previously (220,221).

#### 4.1.2 Data sources

##### **Study 1.**

INS2014 was developed in 2014 by Instituto Nacional de Estatística (Statistics Portugal) and Instituto Nacional de Saúde Doutor Ricardo Jorge – INSA - (National Institute of Health Doutor Ricardo Jorge) as a part of the European Health Interview wave 2 according to the Commission Regulation 141/2013 (222). INS2014 was based on a representative sample (at national and regional levels), of community-dwelling individuals aged 15 years or older. Survey sample was obtained using a multi-stage probabilistic sampling procedure (220). In the first stage, primary sampling units (PSU) corresponding to geographical census sections were selected in each *Nomenclatura das Unidades Territoriais para Fins Estatísticos (NUT) II* region. In the second stage, within each PSU private households were selected by systematic sampling. At the final stage, within each selected household one person respondent was selected based on the “last birthday rule” (222).

INS2014 covered four areas: health status, health determinants, healthcare and socioeconomic background. Data collection were conducted by trained interviewers with experience in health and social surveys. One individual by household was interviewed by face-to-face during the household visit and a sub-sample (6.2%) was surveyed using self-administrated web questionnaire. Detailed information on specific questionnaire areas used in study 1 is available in the result section, chapter 5.1. Survey participation rate was of 80.8%. Achieved sample size was of 18 204 individuals (220).

## **Study 2.**

The INSEF2015 was held in 2015 by INSA in collaboration with the five Regional Health Administrations and the Regional Health Secretariats of the Autonomous Regions of Azores and Madeira and the Norwegian Institute of Public Health as a part of "Improvement of epidemiological health information to support public health decision and management in Portugal" Towards reduced inequalities, improved health, and bilateral cooperation" initiative. INSEF2015 was based on a nationally representative probabilistic sample of non-institutionalized individuals aged 25-74 years resident in Portugal (mainland and autonomos regions) for at least 12 months. Survey sample was selected using a two-stage stratified cluster design. In the first stage, primary sampling PSU were selected in each region and according to degree of urbanization. The PSU corresponded to health centers and respective catchment area. In a second stage, in each selected PSU individuals were selected by simple random sampling from the National Health Users' Registry (221). Survey sample achieved 4911 individuals what corresponded to the participation rate of 43.9%. INSEF2015 combined objective health measurements (antropometric measurements, blood collection) and self-reported data. A structured questionnaire was used to collect social and demographic conditions, vaccine uptake, health status, health determinants and health care (221). Data was collected in the health centre facilities and the interview was conducted by trained registered nurses. Data entry was performed in research electronic data capture software Research Electronic Data Capture (REDCap) (223). Detailed information on the variables used in study 2 are available in the result section-chapter 5.2. For the present study only self-reported data was used.

### **4.1.3 Study population**

For study 1, the focus was on community-dwelling individuals aged  $\geq 65$  years, as they represent one main sub-group for which the influenza vaccine is recommended.

For study 2, the analysis was dedicated to the other high-risk sub-group, namely the ones with chronic conditions. As such, the study population included individuals aged 25-74 years and with self-report of chronic conditions for which the influenza vaccine is recommended (asthma; chronic obstructive pulmonary disease; diabetes; cardiovascular, including stroke, myocardial infarction and arrhythmia, liver and kidney disease). Individuals were considered in the study if the reported date of diagnosis was before 2011, and thus considered in the risk group for the 4 seasons in analysis (2011/12 to 2014/15).

#### 4.1.4 Definitions

##### **Main outcomes**

Study 1: Vaccine uptake in the previous 2 years. An individual was considered as being vaccinated at least once if the answer to the question “*When was the last time you had an influenza vaccine shot?*” (month/year) included years 2013 or 2014. The operational variable vaccinated was dichotomous (yes/no) answer.

Study 2: Repeated vaccination status was accessed through the question “*did you had influenza vaccine shot the 2014/2015 winter?*” (yes/no) combined with the questions “*in the previous 3 winters did you had any influenza vaccine shot?*” (all winters, in one or two winter or not vaccinated). Self-reported vaccination status of respondents in previous seasons was categorized in 3 levels: not vaccinated (unvaccinated in all seasons), occasional (vaccinated 1–3 times over 4 seasons) and repeated (vaccinated in all 4 years).

##### **Independent variables**

For both studies a set of potential vaccine uptake associated factors were selected according to background literature review and availability in the questionnaire. It covered several sociodemographic, health behaviour, health status and use of health services variables (Table 4).

**TABLE 4. LIST OF INDEPENDENT VARIABLES USED IN STUDY 1 AND STUDY 2**

	Definition	Categories	Study 1	Study 2
<b>Demographic</b>				
Age group	Age at time of interview	5 years or 25-64/65-74	X	X
Sex	Sex	Male and female	X	X
Education	Achieved educational level	Primary, secondary, and tertiary (ISCED)	X	X
Marital status	Marital status	Single, married, widow, and divorced	X	X
Household equivalized Income	Family income	Quintile 1(Low)-5(High)	X	X
Cohabitants	Number of cohabitants in the household	Alone, one, and 2 or more	X	X
Urbanization level	Typology of residency area	Urban, semi-urban, and rural	X	X
Birthplace	Place of birth	Portugal, other EU and other outside EU	X	
<b>Health status</b>				
Self reported Health Status	Self-rated health status	Very Good, good, Fair, and Bad/very bad	X	X
Chronic conditions*	Self-reported chronic conditions	None or 1, 2, and $\geq 3$ conditions	X	X
Daily activities	Personal and instrumental activities of daily living score	None, moderate, and severe	X	
<b>Health behaviour</b>				
Smoking status	Tobacco consumption	Current, former and never smoker	X	X
Preventive care (12 months previous to interview)	Hypertension (HTA) and Cholesterol measurement, Prostate-Specific Antigen (PSA) Test, Mammography, Cervical, glucose, Colonoscopy	Yes, no	X	
<b>Health care use</b>				
Primary care visits	GP visit in previous 4 weeks	None, 1, and $\geq 2$ visits	X	X
Other MD specialist	Visits in previous 4 weeks	None, 1, and $\geq 2$ visits	X	X
Outpatient visits		None, 1, and $\geq 2$ visits	X	
Hospitalizations	Number in previous 12 month	s	X	
<b>Social network</b>				
Extent of social network		One, 1 to 2, 3 to 5, and 6 or more	X	
Overall perceived social support		Poor, moderate, and strong support	X	

Legend: X - used in the study; \*chronic condition: study 1- ; study 2-myocardial infarction, stroke, cardiac arrhythmia, diabetes, chronic renal insufficiency, cirrhosis, chronic hepatitis, asthma and chronic obstructive pulmonary disease (all self-reported and diagnosed by a medical doctor).

#### 4.1.5 Statistical analysis

All estimates were weighted to account for different selection probabilities resulted from complex sample design and to match the distribution of Portuguese resident population in terms of geographic region, age group (study 2, INSEF2015) plus education and household size (study 1, INS2014). Results were interpreted considering statistical significant for  $p$ -value  $<0.05$ . Specific statistical analysis are described below:

##### **Study 1 - Determinants of influenza vaccine uptake**

All analysis developed within study 1 was stratified by sex. Reasons for this option are provided in chapter 5.1.

Taking in consideration the different social ecologic model (SEM) levels and correspondent variables, descriptive analysis provided the proportion in each of the independent variables.

Bivariate analysis was conducted to estimate VC and prevalence ratios (PR) of IV uptake and respective 95% confidence intervals. To evaluate the association of each individual independent variable and the IV uptake design-adjusted Rao–Scott version of Pearson’s chi-square test (224) was used.

Two set of multivariate analysis were done to evaluate the association between the identified factors and the IV uptake. First multivariate analysis intended to evaluate the association of each variables set of SEM level (individual, interpersonal, organizational, community and policy) with the IV uptake. As such, five age adjusted Poisson regression models were fitted, each one included the variables within specific SEM level. The Poisson regression model was selected, given the cross-sectional nature of the study and thus allowing the estimation of prevalence ratio directly from the exponentiation of model coefficient (225).

Second, a full Poisson regression model using all SEM levels sets variables was adjusted and compared with the model without each SEM level and respective variables to evaluate the significance of each level in IV prediction. This approach allowed estimating the marginal contribution of each SEM level to the full model of IV uptake. According to Ohri-Vachaspi et al (226), for these objectives, this approach is better than the traditional gradual addition of each level, and respective change in explanatory power of the model evaluation. These authors considers that this may introduce bias, as first entered levels may not be independent from the effect of introduction of remain levels. The SEM level marginal contribution significance was evaluated using likelihood ratio test between the full model and the model without the

SEM level being evaluated. The SEM level marginal contribution of each SEM level was measured by magnitude of reduction in pseudo R square proposed by Cameron and Windmeijer (227) based on weighted deviance statistic.

Statistical analysis was run using *survey* package of R 3.5.1 software (228) and *svy* module of STATA 15® software (229).

## **Study 2 - Coverage of repeated vaccination and associated factors**

Descriptive statistics (counts and proportions) were computed to describe study participants, including seasonal influenza vaccine coverage in 2014/15 season for overall sample and by specific chronic condition.

Proportion of repeatedly and occasionally vaccinated was estimated for overall sample and stratified by socioeconomic characteristics. Bivariate analysis was done to examine the association between the influenza vaccination status and the independent factors using a design-adjusted Rao–Scott version of Pearson’s chi-square test (224).

A multinomial logistic regression model was then applied to estimate adjusted odds ratios (OR) of repeated and occasional influenza vaccination against non-vaccinated in the four seasons. Data analysis was carried out using [SVY] package of Stata 15® software (229) and 95% confidence intervals were computed.

## **4.2 Influenza vaccine effectiveness**

Within objective 2, two studies were developed to answer the specific objectives: 2.1- influenza vaccine effectiveness against medically attended influenza (**study 3**) and 2.2- influenza vaccine effectiveness against hospitalized influenza (**study 4**). Both studies were developed in the ambit of European multicentric IVE studies, Influenza-Monitoring Vaccine Effectiveness (I-MOVE) (24,230) network, with Portuguese contribution on primary care medically attended influenza (study 3- project EuroEVA (130)) and hospitalized influenza (study 4 - project EVAHospital).

### **4.2.1 Study design**

For both studies, the test negative design (TND) was used. This design, consists in the comparison of the seasonal influenza VC between laboratory confirmed influenza cases and laboratory influenza-negative patients (controls). Full generic protocols of both IVE studies are available elsewhere (131,203).

In summary, the implementation of this design consists in the selection of patients based on clinical symptoms of influenza in primary care (influenza like illness - ILI) and in the hospital settings (severe acute respiratory infection- SARI). Clinical influenza



patients were swabbed and after laboratory detection were classified as cases, those positive for any influenza virus sub(type), and controls those negative for any influenza virus (sub)type. More specific details EuroEVA and EVAHospital studies will be described in the following sections.

#### 4.2.2 Sampling

**Study 3:** A sample of approximately 144 GP was constituted based on Rede Médicos Sentinela (GP Network) (231) and others GP's. ILI patients were identified among patients that consulted a GP with respiratory infection sign and symptoms. All participating GPs work in a Health Centers of the National Health Service (Ministry of Health) and have a stable list of patients. The participating GPs cover all Mainland Portugal and autonomous regions. All ILI patients aged 60 or more years were included in the study. A systematic sampling method was used for the recruitment of patients with less than 60 years of age. This procedure consists on the selection, by each GP, of the first two ILI cases of each week. In order to avoid biases regarding the weekday, the first day of the week for each GP was randomly assigned.

**Study 4:** SARI patients were recruited at two collaborating hospitals, the Centro Hospitalar Universitário Lisboa Central (CHULC) and Centro Hospitalar de Setúbal (CHS). The systematic SARI identification occurred in the emergency room or in medicine ward or intensive care unit (ICU), depending on the hospital.

#### 4.2.3 Study population

Both studies were based on community-dwelling individuals with no contra-indication for influenza vaccination who consult a GP if they develop ILI or were hospitalised with SARI.

Study 3 is focused in all aged individuals, with particular focus in the aged  $\geq 60$  years, for which the vaccine is highly recommended. Study 4 is restricted to the population aged  $\geq 65$  years.

Exclusion criteria: institutionalized, with contra indication for vaccine uptake, swabbed with more than 7 days after symptoms onset, had previous influenza infection in the season and nosocomial influenza.

#### 4.2.4 Study period

Study 3 comprised seasons 2010/11 to 2017/18 and study 4, seasons 2015/16 to 2017/18.

In each season, ILI and SARI patients were recruited 1.5 to 2 months after the influenza vaccination campaign started. The study period ended in week 20 or when influenza activity was below baseline threshold and there was no detection of influenza positive cases for two consecutive weeks.

#### 4.2.5 Definitions

##### **Clinical influenza signs and symptoms**

Study 3 used ILI patient case definition established by the European Commission implementing decision “On the communicable diseases and related special health issues to be covered by epidemiological surveillance as well as relevant case definitions” (232). Namely, *ILI patient* was defined as a patient that consults a participating GP, presenting a sudden onset of symptoms and at least one in three respiratory symptom or sign (cough, sore throat and shortness of breath) and one in four systemic symptom or sign (fever or feverishness, malaise, headache and myalgia).

*SARI patients*: hospitalised patient (admission for  $\geq 24$  hours) with at least one systemic symptom or sign (fever, malaise, headache, myalgia or deterioration of general condition) and at least one respiratory symptom or sign (cough, sore throat or shortness of breath) (233).

##### **Main Outcome**

Study 3: Medically attended influenza at primary care - ILI laboratory - confirmed influenza cases. Type/subtype influenza specific outcomes were also analysed.

Study 4: Hospitalized influenza - SARI laboratory - confirmed influenza cases. Type/subtype influenza specific outcomes were also analysed.

Influenza diagnosis was performed in all recruited patients using RT-PCR. ILI swabs were analysed at the National Reference Laboratory for Influenza and other Respiratory Virus at INSA and SARI swabs in the Laboratório de Biologia Molecular (CHLC) and Laboratório de Imunologia e Biologia Molecular (CHS).

##### **Main Exposure**

The exposure of interest was the seasonal influenza vaccine uptake. Individuals were considered as vaccinated if the vaccine uptake occurred 14 days before the clinical illness signs and symptoms onset.

Inoculation with approved seasonal influenza vaccine was ascertained by the health professional by consulting of the vaccination registries in the clinical process or Health Data Platform (PDS). If the vaccination was performed outside the National Health

System, an interview of the patient and/or his/her relatives allowed collecting the vaccination status.

### **Other independent variables**

Potential confounders were collected in both studies (Table 5).

#### **4.2.6 Data collection**

In both setting, data was collected using a standardized questionnaire form prepared for optical recognition (see annex questionnaire). The source(s) of data included clinical medical records, the PDS, interview with patient or his/her family and hospital laboratory.

#### **4.2.7 Statistical analysis**

In both studies 3 and 4, cases and controls were compared using the chi-square test, Fisher's exact test, t-test or the Mann-Whitney test (depending on the nature of the variable and the sample size).

Vaccine effectiveness was estimated using  $1 - \text{OR}$  of vaccine uptake between cases and controls, and exact 95% confidence interval was computed around the point estimate. IVE was represented as percentage. Multivariable conditional logistic regression analysis was conducted to control for confounding, considering week (study 3) or month (study 4) of onset as the matching variable. To select potential confounding, in study 3, a theoretical model of causal relation between influenza vaccination and infection was developed using directed acyclic graphs (DAG).

Specific DAG was build considering the results obtained in studies 1 and 2 (factors associated to influenza vaccine uptake), and a systematic review (on risk factors for influenza) (7). As mentioned in methods of study 1 and 2, the set of potential IV associated factors were derived from review from several previous studies, developed in different countries and from meta-analysis. As such, the analysed variables were the ones that consistently were found as associated to IV uptake. Considering that results from studies 1 and 2 derived from cross-sectional studies, and the causal effect is difficult to infer from this type of study design, only adjusted statistical significant variables were considered as "causal". This is assuming the premise that causal relations are statistically associated. Additionally, although it was based on cross-sectionals studies, most variables were either constant to the individuals (such as sex) or were related to past experience, such as number of GP visits in the previous year or 3 months, and thus represent previous "exposure" to vaccine uptake. These results allowed connecting the arrows from the factor to influenza vaccine uptake and

medically attended influenza, assuming a direct effect of the variable on exposure (vaccine) on the outcome infection. The minimum set of variables needed to adjust for confounding was established using the back-door approach (234).

**TABLE 5. POTENTIAL CONFOUNDING FACTOR COLLECTED IN EUROEVA (STUDY 3) AND EVAHOSPITAL (STUDY 4)**

Variable	Definition	Study 3	Study 4
Age	Age at the time of participation		
Sex	Male or female		
Chronic conditions	Diabetes: if treated for insulin or non-insulin-dependent diabetes; Cardiovascular disease (congenital heart disease, hypertensive heart disease, ischemic heart disease, chronic heart failure); Chronic renal disease (chronic renal failure and nephrotic syndrome); Chronic hepatic disease (cirrhosis, biliar atresia and chronic hepatitis); Obesity BMI $\geq$ 30; Chronic respiratory disease (asthma, chronic bronchitis, emphysema, bronchopulmonary dysplasia, cystic fibrosis, pneumoconiosis and pulmonary fibrosis) ; Congenital or acquired immunodeficiency (conditions that suppress the immune function due to underlying disease and/or therapy, e.g. chemotherapy, HIV infection); Neuromuscular disease.	X	X
Severity of chronic condition	Severity was measured by the number of hospital admissions due to underlying chronic conditions in the 12 months prior to inclusion in the study.	X	X
Smoking	Smoking history coded as follows: never-smoker, former smoker (stopped smoking at least one year before inclusion in the study), current smoker.	X	X
Previous vaccinations	Vaccination against seasonal influenza in previous season	X	X
Dependency	Low functional status on adults was defined as needing help to bath or Barthel index (235)	X	X
GP consultations	The number of all GP visits in the 12 months before inclusion in the study was recorded.	X	X
Antiviral administration	Use of antivirals was documented: type and date of administration.	X	X
Statin	Use of statin and date at the start of uptake.	X	X
Pneumococcal vaccine	Uptake of Pneumococcal Conjugate Vaccine or Pneumococcal polysaccharide vaccine vaccine		X
Hospital consultations	The number of all hospital visits in the 3 months before inclusion in the study		X
ICU	Admission in ICU during the hospital stay		X

### 4.3 Impact of the influenza vaccination strategy

To achieve specific objectives under objective 3, two studies were developed. **Study 5**, that estimated the impact of IV strategy in primary care medically attended influenza and **study 6**, that aimed to estimate the IV strategy impact in more severe influenza outcomes, namely, hospitalizations and intra-hospital deaths. Study 5 is a joint collaboration of 3 countries (Portugal, Spain and The Netherlands), that resulted in a common protocol to measure the impact of influenza vaccination strategy in Europe (236). Within this thesis, the methods for measuring the impact of the influenza vaccination strategy in Portugal are fully described. Detailed information on the methods for remain countries can be found elsewhere (236).

#### 4.3.1 Study design

For measuring the impact of influenza vaccination strategy (**objective 3**), the definition of vaccine effects suggested by Halloran (2006) (237) and the reflections on vaccine effects and impact of vaccination programmes by Hanquet et al. (2013) (15), were adopted. Taking in consideration Figure 5 of this thesis, the impact of influenza vaccination programmes consists in the comparison of the risk (incidence rate) of influenza in a population with an influenza vaccination programmes ( $R_{IVP}$ ) in place (or intervention population 1) with a hypothetical susceptible population that has never been exposed to the intervention (or control population 2) ( $R_{No\ IVP}$ ). The prevented fraction (PF) in such situation would be (Equation 4.3.1):

**Equation 4.3.1**  $PF = \frac{R_{No\ IVP} - R_{IVP}}{R_{No\ IVP}}$

where

$R_{No\ IVP}$ - the influenza risk in a population with no influenza vaccination programme and

$R_{IVP}$ - the influenza risk in a population with influenza vaccination programme

The previous formula is equivalent to Equation 4.3.2:

#### Equation 4.3.2

$$PF \times R_{No\ IVP} = R_{No\ IVP} - R_{IVP} \Leftrightarrow R_{IVP} = R_{No\ IVP} (1 - PF) \Leftrightarrow R_{No\ IVP} = R_{IVP} / (1 - PF)$$

Considering that the risk of influenza in a population with no influenza vaccination program is:

**Equation 4.3.3**  $R_{No\ IVP} = N / Pop$

where

N is the number of influenza related outcomes in the population (Pop) without influenza vaccine programme (Pop)

Equation 4.3.2 could be written as (Equation 4.3.4):

**Equation 4.3.4**  $\frac{N}{Pop} = \frac{n/Pop}{(1-PF)}$

where

n is the number of observed influenza related outcomes in the population (Pop) with IV programme (Pop)

Assuming that both population have the same dimension, Equation could be simplified to (Equation 4.3.5):

**Equation 4.3.5**  $N = \frac{n}{(1-PF)}$

The number of averted events (NAE) would be the difference of influenza cases in a population without influenza vaccination program (N) and with an influenza vaccination program (n) (Equation 4.3.6).

**Equation 4.3.6**  $NAE = N - n \Leftrightarrow NAE = \frac{n}{(1-PF)} - n$

As expressed by Hanquet et al. (15), if there is no indirect effect, the PF may be estimated as VC x IVE. Looking to Equation 4.3.6 may be written as (Equation 4.3.7):

**Equation 4.3.7**  $NAE = \frac{n}{(1-PF)} - n \Leftrightarrow NAE = \frac{n}{1-(VC \times IVE)} - n \Leftrightarrow NAE = n \times \frac{VC \times IVE}{1-(VC \times IVE)}$

Overall effect of vaccine strategy was then measured through estimating the number of averted cases by vaccination (equation 4.3.7) and prevented fraction (equation 4.3.8). The number of individuals needed to vaccinate (NNV) to prevent an additional IRO was also estimated (equation 4.3.9) (236):

**Equation 4.3.7**  $Averted\ (NAE) = n \times \frac{IVE \times VC}{1-(VC \times IVE)}$

**Equation 4.3.8**  $PF = NAE / (n + NAE)$

**Equation 4.3.9**  $NNV = 1 / (IVE \cdot N / Pop)$

Where

n – Influenza related outcome (observed)

IVE – Influenza vaccine effectiveness

VC – Vaccine coverage

Pop- Population

Derived from equation 4.3.7, to estimate averted cases there is need of data on i) vaccination coverage (VC), ii) influenza vaccine effectiveness (IVE) and iii) influenza related outcome (n) (burden in medically attended in primary care, hospitalizations and mortality) observed in a presence of vaccination program.

#### 4.3.2 Study population

The impact of IV strategy was estimated for all population aged  $\geq 65$  years (**study 5** and **study 6**) and for population  $< 65$  years with chronic conditions for which the vaccine is recommended (**study 6**).

#### 4.3.3 Study period

For both studies, three consecutive seasons were analysed, namely, seasons 2015/16 to 2017/18 (study 5) and seasons 2014/15 to 2016/17 (study 6). Specific periods covered in each study are detailed in chapter 5.3.

#### 4.3.4 Definitions

##### **Influenza related outcome in the presence of a vaccination program (n)**

Within objective 3, several influenza related outcomes were analysed, from milder to more severe ones. The influenza related outcomes that were used along this study were selected considering the target population (community dwelling) and the outcomes of IVE estimates (medically attended influenza and hospitalized influenza). The term influenza related outcomes refers to morbidity or mortality indicators that were estimated using indirect/statistical methods and intends to estimate associated influenza burden. In essence, it uses clinical (sign and symptoms) and laboratory confirmed- influenza indicators, namely:

- *Medically attended influenza* in primary care: proportion of positive cases of patient that consults a GP presenting influenza signs and symptoms according to the EU ILI definition (232). Influenza positivity was determined using RT-PCR.
- *Influenza Severe Acute Respiratory Infections (SARI)*: proportion of positive cases of patient hospitalised for  $\geq 24$  hours with SARI code (International Classification of Disease -ICD- 9<sup>th</sup> or 10<sup>th</sup> version) as main diagnosis (listed in Table 6). Influenza positivity was determined using RT-PCR.
- *Influenza SARI with chronic condition*: proportion of positive cases of patient with SARI with a secondary diagnosis with an ICD 9<sup>th</sup> or 10<sup>th</sup> code for a chronic condition for which the vaccine is recommended (list in Table 7). Influenza positivity was determined using RT-PCR.
- *Influenza SARI death*: proportion of positive cases of patient with SARI with a discharge code of death. Influenza positivity was determined using RT-PCR.

**TABLE 6. LIST OF ICD 9<sup>TH</sup> AND 10<sup>TH</sup> VERSION CODES FOR SARI**

Category	Morbidity	ICD-9	ICD-10
Influenza like illness	Cough	786.2	R05
	Difficulty breathing	786.05	R06
	Sore throat	784.1	R07.0
	Dysphagia	787.20	R13
	Fever	780.6	R50.9
	Headache	784.0	R51
	Myalgia	729.1	M79.1
	Fatigue/malaise	780.79	R53.1, R53.81, R53.83
Cardiovascular diagnosis	Acute myocardial infarction or acute coronary syndrome	410-411, 413-414	I20-23, I24-25
	Heart failure	428 to 429.0	I50, I51
Respiratory diagnosis	Emphysema	492	J43.9
	Chronic obstructive pulmonary disease	496	J44.9
	Asthma	493	J45
	Myalgia	729.1	M79.1
	Dyspnoea/respiratory abnormality	786.0	R06.0
	Respiratory abnormality	786.00	R06.9
	Shortness of breath	786.05	R06.02
	Other respiratory abnormalities	786.09	R06.00, R06.09, R06.3, R06.89
Infections	Pneumonia and influenza	480-488.1	J09-J18
	Other acute lower respiratory infections	466, 519.8	J20-J22
	Viral infection, unspecified	790.8	B34.9
	Bacterial infection, unspecified	041.9	A49.9
	Bronchitis	490, 491	J40, 41
Inflammation	SIRS non infectious without acute organ dysfunction	995.93	R65.10
	SIRS non infectious with acute organ dysfunction	995.94	R65.11
Diagnoses related to deterioration of general condition or functional status	General physical deterioration, lethargy, tiredness	780.79	R53.1, R53.81, R53.83
	Anorexia	783.0	R63.0
	Feeding difficulties	783.3	R63.3
	Abnormal weight loss	783.21	R63.4
	Other symptoms and signs concerning food and fluid intake	783.9	R63.8
	Disorientation/Altered mental status	780.97	R41.0
	Dizziness and giddiness	780.4	R42
	Infective delirium	293.0, 293.1	F05
	Coma	780.01	R40.2
	Transient alteration of awareness	780.02	R40.4
	Other alteration of consciousness (Somnolence, stupor)	780.09	R40.0, R40.1
	Febrile convulsions (simple), unspecified	780.31	R56.00
	Complex febrile convulsions	780.32	R56.01

*\*SIRS: Systemic inflammatory response syndrome*



**TABLE 7. LIST OF ICD 9<sup>TH</sup> AND 10<sup>TH</sup> VERSION CODES FOR CHRONIC CONDITIONS**

	<b>ICD 9th version</b>	<b>ICD 10th version</b>
Respiratory	011, 490–511, 512.8, 513–517, 518.3, 518.8, 519.9, 714.81	A15, J40-47, J60-94, J96, J99, J182, M34.81, M05.10
	746.9	Q24.9
Cardiovascular	402.0-402.91	I11.0-I11.9
	428.42, 428.32, 482.22	I50.22, I50.32, I50.42
	412.0-412.9, 413.0-413.9, 414.0-414.9	I25.2, I20.8, I20.1, I20.9, I25.0-I25.9
Renal	581.0-581.9, 585.0-585.9	N18, N04
Kidney	571.0-571.9	K70, K74, K72.1
	576.2	
Hematologic	282.4, 282.5, 282.6	D56, D57
Imunocompromised	042, 279, V08, V42	B20, D80-84, D89.8-9, Z21, Z94
Diabetes mellitus	250	E10-11; Z94.0-Z94.4, Z94.6-Z94.9
Genetic conditions	273.4	E88.01
Obesity	278.00, 278.01, 278.03	E66.01, E66.2, E66.9

### **Influenza vaccination status**

Seasonal influenza vaccine coverage: "proportion of vaccinated" individuals whose vaccination status was either self-reported or reported by proxy and the inoculation was through a "shot".

The list of relevant chronic condition for influenza vaccination (11,104) that are collected from a panel of family households (Em Casa Observamos Saúde -ECOS panel includes asthma; chronic obstructive pulmonary disease (chronic bronchitis, pulmonary emphysema); diabetes; obesity; ischemic heart disease (coronary heart disease, angina pectoris); liver disease and kidney disease.

### **Influenza vaccine effectiveness**

Reduction (in percentage) of influenza related outcome due to vaccine uptake (189).

## **4.3.5 Data Sources**

In Table 8, a correspondence of the influenza outcome and data source is provided:

**TABLE 8. Data sources used for impact studies (study 5 and study 6)**

Parameter	Data source
Number of medically attended influenza in primary care	<ul style="list-style-type: none"> <li>• Influenza surveillance systems, primary care influenza like-illness consultations - Rede Médicos Sentinela (231)</li> <li>• National Reference Laboratory for Influenza and other Respiratory Virus (238,239)</li> </ul>
Number of influenza hospitalizations	<ul style="list-style-type: none"> <li>• Hospital discharge database (Grupo de diagnóstico Homogéneo- GDH)</li> <li>• National Laboratory Network for Influenza (240)</li> </ul>
Number influenza intra-hospital deaths	<ul style="list-style-type: none"> <li>• Hospital discharge database (Grupo de diagnóstico Homogéneo- GDH)</li> <li>• National Laboratory Network for Influenza (240)</li> </ul>
Vaccine coverage	<ul style="list-style-type: none"> <li>• Survey to ECOS panel - panel of family household (241)</li> </ul>
Influenza vaccine effectiveness	<ul style="list-style-type: none"> <li>• I-MOVE network (131,230);</li> <li>• Meta-analysis (141) and</li> <li>• Spanish IVE study (242)</li> </ul>

### 4.3.6 Sampling and data collection

#### **Influenza related outcomes**

##### *Number of medically attended influenza in primary care*

The primary care influenza like-illness consultations derived from data collected by the GP surveillance network, Rede Médicos Sentinela. This network was based on voluntary GPs participation and covers Portugal Mainland and Autonomous regions. In 2015/16-2017/18 influenza seasons the number of participants varied between 124 and 145 GPs (243,244). All participating GPs worked in a public Health Centres of National Health Service (Ministry of Health) and had a stable list of patients.

Epidemiological and laboratory data on medically-attended ILI were obtained through the National Influenza Surveillance System, namely, the Rede Médicos-Sentinela and the National Reference Laboratory for Influenza and Other Respiratory Virus of INSA (231,238,239,243,244). Participating GPs reported all cases of ILI from their patient lists on a weekly basis using a standardized form (via web or paper).

#### *Number of hospitalized SARI and intra-hospital SARI deaths*

Hospitalized SARI and intra-hospital SARI deaths were retrieved from the National Hospital Discharge Database. This database covers all public hospitals in Portugal mainland and that corresponds to approximately 79% of all hospital admissions (245).

The data are anonymous, each record corresponds to discharge episode and includes information on principal and secondary diagnosis, procedures during hospitalization, type of admission, length of stay, outcome at discharge as well as some patient socio-demographic information (age, sex, region of residence).

#### *Laboratory confirmed cases*

Influenza positivity derived from laboratory databases collected at National Reference Laboratory for Influenza and other Respiratory Virus (for medically attended influenza) and National Laboratory Network for Influenza (for hospitalized influenza). The first consists in the laboratory component of the national influenza surveillance and receives swabs from emergency rooms and primary care services (Rede médicos sentinela and EuroEVA project). The National Laboratory Network for Influenza collects influenza positivity results from 18 hospitals distributed at national level.

Health professionals participants in the surveillance system collect swabs and epidemiological information using a standard form (paper or excel file).

#### **Vaccine coverage**

As referred, the vaccine coverage was estimated by applying a survey to the ECOS panel (Em Casa Observamos Saúde). ECOS panel is composed by a sample of households, population based dual-frame with landline or mobile telephone in Portuguese mainland population. Landline telephone numbers are randomly selected from the telephone contact list/or random digit dialling and mobile phone numbers are generated through random digit dialling. ECOS panel is a nationally representative probability sample of households stratified by the five NUT II regions of mainland Portugal with homogeneous allocation of sampling units, with approximately 1000 households.

Influenza vaccination status and other relevant socio-demographic, health status, health seeking behaviour was collected using a standardized questionnaire (100). Data was collected by trained interviewers through Computer Assisted Telephone Interview of one element of each household aged 18 or more years.

### **Influenza vaccine effectiveness**

Influenza vaccine effectiveness data were derived from the European primary care IVE study, I-MOVE network (study 5) and meta-analysis (study 6). I-MOVE network study is described in detail elsewhere (131).

#### **4.3.7 Statistical analysis**

##### **Influenza related outcomes**

*Number of medically attended influenza cases* in primary care was estimated by multiplying end of season cumulative ILI incidence rate by the season overall influenza positivity rate and extrapolating to population figures. The denominators for primary care ILI rates estimates (population under observation) were obtained as a sum of the patients lists of Sentinel GPs who reported cases (or indicated no cases to report) in the respective season (238,239). The proportion of positive for influenza in primary care settings in respective season, provided by the National Reference Laboratory for Influenza, and resident population figures were provided by Statistics Portugal (238,239,246).

*Number of SARI Influenza hospitalizations* were obtained by multiplying the weekly number of SARI patients hospitalized during the epidemic period by the weekly proportion of positive hospitalized patients for influenza, obtained from Portuguese laboratory network for the diagnosis of influenza (238).

*Number of SARI Influenza deaths* were estimated using the discharge outcome information. The number of deaths occurred in patients hospitalized with SARI diagnosis during the study period was multiplied by the proportion of hospitalized patients influenza positive, obtained from the Portuguese laboratory network for the diagnosis of influenza (238).

##### **Vaccine coverage**

In each season, the proportion of individuals vaccinated was weighted to account for different selection probabilities resulted from complex sample design and to match the distribution of mainland Portuguese resident population in terms of geographic region and age group. Confidence intervals, 95%, were computed around point estimates using logit transformation (247).

##### **Influenza vaccine effectiveness**

In Portugal due to the small sample size it is not possible to have precise estimate of IVE. To overcome this limitation, we used pooled European IVE estimates or derived

from meta-analysis. In order to reflect these IVE estimates at national level and for each season we used information on the distribution of influenza virus (sub)type. For the different influenza outcomes we used different IVE estimates/ data sources and influenza laboratory data.

#### *Medically attended influenza in primary care*

Multicentre (sub)type IVE estimates among those aged 65 and older pooled across the 3 seasons included in the I-MOVE (Table 9) were weighted by the distribution of circulating influenza (sub)type in each season in Portugal. Information on circulating influenza (sub)type detected in primary care settings was provided by the National Reference Laboratory for Influenza of the INSA (Table 10) (238,239). Confidence intervals, 95%, for IVE weighted estimates were computed using a meta-analysis approach.

**TABLE 9. POOLED VE RESULTED FROM THE IMOVE MULTICENTER PRIMARY CARE BASED STUDY**

<b>Seasons included</b>	<b>Type/subtype</b>	<b>IVE (95% CI)</b>
2015/16-2017/18	A(H1N1)pdm09	42.8 (19.6; 59.3)
2016/17-2017/18	A(H3N2)	8.4 (-13.1; 25.8)
2015/16-2017/18	B	21.3 (0.9; 37.5)

**TABLE 10. DISTRIBUTION OF CIRCULATING INFLUENZA (SUB)TYPES IN PORTUGAL, ALL AGES**

<b>Seasons</b>	<b>A(H1N1)pdm09 (%)</b>	<b>A(H3N2) (%)</b>	<b>B (%)</b>
2015/16	90.4	1.3	8.3
2016/17	0.2	99.6	0.2
2017/18	20.0	14.0	66.0

#### *SARI influenza hospitalizations*

Meta analysis type/subtype IVE estimates (141) (Table 11) were weighted by the distribution of circulating influenza type/subtypes in hospital setting each season in Portugal (Table 12). 95% confidence intervals for IVE weighted estimates were computed.

**TABLE 11. META ANALYSIS TYPE/SUBTYPE IVE ESTIMATES FOR ≥65 YEARS AND <65 YEARS**

	<b>≥65 years</b>	<b>&lt;65 years</b>
Type/sub-type	IVE (95%CI)	IVE (95%CI)
AH1pdm09	54% (IC95%: 26 to 82)	55% (IC95%: 34 to 76)
AH3N2 (all)	33% (IC95%: 21 to 45)	50% (IC95%: 38 to 62)
AH3N2 (match):	43% (IC95%: 33 to 53)	59% (IC95%: 38 to 80)
AH3N2 (unmatch)	14% (IC95%: -3 to 30)	46% (IC95%: 30 to 61)
B	31% (IC95%: 11 to 51)	45% (IC95%: 8 to 81)

**TABLE 12. DISTRIBUTION (%) OF CIRCULATING INFLUENZA TYPE/SUBTYPES IN PORTUGAL IN HOSPITAL SETTINGS**

<b>Seasons</b>	<b>A(H1N1)pdm09 (%)</b>	<b>A(H3N2) (%)</b>	<b>B (%)</b>
2014/15	8.6	23.2*	68.2
2015/16	79.9	1.8*	18.3
2016/17	0.2	98.9	0.9

\*AH3 mismatch between vaccine and circulating virus in 2014/15 and 2015/16 seasons

### *SARI influenza deaths*

Vaccine effectiveness against intra-hospital deaths of 56% (14% to 77%) reported by Casado et al. (242) for the Spanish population was used for all high-risk group. This option derived from the adequacy between the influenza related outcome and the IVE outcome.

### **Uncertainty**

For NAE, PF and NNV final estimates, the input parameters (n, IVE, VC) uncertainty was taken in account using Monte Carlo simulations. For that, empirical distributions for influenza related outcomes, IVE and VC were constructed. The distribution parameters were derived using the point estimates and the 95% confidence intervals of input parameters.

First, we constructed empirical distributions for all input parameters, i.e., number of influenza-related outcomes, VC and IVE.

For the number of influenza-related events (count data) we assumed a Poisson distribution.

To obtain empirical distribution of IVE we assumed a Normal distribution for  $\log(1-IVE)$ . This option was chosen since IVE estimates are obtained as  $IVE=(1-Odds\ ratio\ (OR))$ , where OR was estimated by logistic regression model. OR is obtained as  $OR=\exp(\beta)$ , where  $\beta$  represents coefficient from logistic regression model. We transformed IVE into  $\widehat{\beta}_{ve} = \log(1 - \widehat{IVE})$  and IVE 95% confidence interval upper  $\widehat{IVE}(u)$  and lower  $\widehat{IVE}(l)$  bounds into  $\widehat{\beta}_{ve(l)} = \log(1 - \widehat{IVE}(u))$  and  $\widehat{\beta}_{ve(u)} = \log(1 - \widehat{IVE}(l))$ , respectively. We computed a standard error  $SE_{\beta_{ive}} = \frac{\widehat{\beta}_{ve(u)} - \widehat{\beta}_{ve(l)}}{2 * Z_{0.975}}$ , where  $Z_{0.975}$  represents the 0.975 cumulative probability quantile of standard Normal distribution, and generated pseudo-random numbers from Normal distribution:

$$\widehat{\beta}_{ive} \sim Normal(\widehat{\beta}_{ive}, SE_{\beta_{ive}}).$$

Simulated values of  $\widehat{\beta}_{ive}$  were transformed back to original scale using following formula:  $IVE = 1 - \exp(\widehat{\beta}_{ive})$ .

For VC, since originally VC was estimated from a complex survey and the 95% confidence interval was computed using logit transformation (247), we transformed VC into  $\widehat{\beta}_{vc} = \log\left(\frac{\widehat{VC}}{1-\widehat{VC}}\right)$ . Lower and upper limits of VC confidence interval were transformed as  $\widehat{\beta}_{vcl} = \log\left(\frac{\widehat{VC}(l)}{1-\widehat{VC}(l)}\right)$  and  $\widehat{\beta}_{vcu} = \log\left(\frac{\widehat{VC}(u)}{1-\widehat{VC}(u)}\right)$  to estimate  $SE_{\beta_{vc}} = \frac{\widehat{\beta}_{vcu} - \widehat{\beta}_{vcl}}{2 * Z_{0.975}}$ , where  $Z_{0.975}$  represents a quantile of standard Normal distribution.

We generated pseudo-random numbers from Normal distribution  $\widehat{\beta}_{vc} \sim Normal(\widehat{\beta}_{vc}, SE_{\beta_{vc}})$  and applied inverse transformation to return to original scale.

$$VC = \frac{\exp(\widehat{\beta}_{vc})}{1 + \exp(\widehat{\beta}_{vc})}.$$

We draw 10 000 samples of number of influenza-related events, IVE and VC distributions and used them to construct empirical distributions of NAE, NNV, and PF. The 2.5% and 97.5% percentiles of these empirical distributions were used as lower and upper limits of the 95% confidence intervals for NAE, NNV, and PF.

## 4.4 Ethical and data protection issues

This project was a human based research, that deals with sensitive health information and as such several ethical issues related to autonomy, privacy, benefit and no harm of the participants need to be accounted for. In addition to its nature, extra ethical care was needed given that intends to evaluate a pharmaceutical product.

The scientific protocols of EuroEVA and EVA Hospital were submitted and approved by the Ethical Committee (EC) of INSA. EVA Hospital was also submitted and approved by the EC of CHULC and of CHS. The study start was dependent on their recommendations to guide the research both in the national and specific setting, allowing the study development in line with research best practice. Regarding autonomy, specific written informed consents were elaborated and included the authorization to perform further analysis regarding to influenza studies. This consent had a detached information flyer with study objectives and their right to redraw from the study. Privacy was assured through anonymization and creation of a participant code, with the link to the personal information only known by the medical staff. In the end of the study, the decoding key is destroyed.

EuroEVA, EVA Hospital and ECOS were submitted and approved by the National Data Protection Committee.

Finally, and in what relates to the evaluation of pharmaceutical products (with commercial objectives), it is of major importance to evaluate vaccination, using independent and with no conflict of interest financed research teams, as the present, reinforcing the scientific and public trust in research results.



## 5 Results

### 5.1 Influenza vaccine coverage and associated factors

In order to answer to the research questions “*what is the influenza vaccine coverage in the high-risk population, on a given seasons?*” and “*what are the factors associated with influenza vaccine uptake in one season and continuously over several seasons?*” two studies were conducted.

First study, “*Understanding influenza vaccination among Portuguese elderly: the social-ecological framework*”, tackles both questions but restricted to older adults, aged 65 and more years.

The second study “*Factors associated to repeated influenza vaccination in the Portuguese adults with chronic conditions*” is dedicated to adults aged 24-74 years with chronic condition. As such, it covers most high-risk individuals for which the vaccine is recommended. It also addresses a question that is not often studied, which is the regular, i.e., yearly, influenza vaccine uptake.



# **Understanding influenza vaccination among Portuguese elderly: the social-ecological framework**

Machado A <sup>1,2</sup>, Santos AJ <sup>1,2</sup>, Kislaya I <sup>1,2</sup>, Larrauri A <sup>3</sup>, Nunes B <sup>1,2</sup>

1 - Departamento de Epidemiologia, Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa, Portugal

2 - NOVA National School of Public Health, Public Health Research Centre, Universidade NOVA de Lisboa, Lisbon, Portugal

3 - National Centre of Epidemiology, Institute of Health Carlos III. CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

## **Abstract**

In a context of lower than targeted influenza vaccination (IV) coverage, identifying factors associated with IV uptake is essential to improve population coverage. Having the social ecological model (SEM) as a framework, this study intended to identify and quantify the SEM levels associated with seasonal IV uptake in the Portuguese population aged 65 and more years.

Data from the National Health Survey was restricted to individuals aged  $\geq 65$  years. Twenty-three independent variables were allocated to the SEM levels: individual, interpersonal, organizational, community and policy. Sex-stratified and age-adjusted analysis using Poisson regression were performed for each level and for a fitted full model. Relative reduction in pseudo-R magnitude measured each level marginal contribution.

For men and women, older groups (85+ vs. 65-69; men, PR=1.59 and women, PR=1.56); having 3+ chronic conditions (men, PR=1.39 and women, PR=1.35); previous 4 weeks GP and outpatient visits were associated to higher IV uptake. For men, only 2 SEM levels were associated (individual and organizational) while for women the community level was also relevant. Main marginal contribution came from individual (17.9% and 16.3%) and organizational (30.7% and 22.7%) levels.

Besides individual characteristics, like age and health status - known determinants of IV uptake - this study highlights the importance of access and use of health care services for adoption of IV preventive measure. Moreover, it evidences a sex differential behaviour that should be accounted for in the definition of the IV campaign strategy.

**Keywords:** influenza vaccine, social ecologic model, older adults

## **Background**

Influenza vaccination is the main prevention measure adopted to prevent influenza infection, to reduce influenza health care impact on services and influenza-related morbimortality (Anon 2012). Considering the potential benefits for high-risk individuals, the World Health Organization established a 75% target of vaccine coverage for 2014; motion reaffirmed in 2009 by the European Council (EC 2009).

Following the World Health Organization recommendations (World Health Organization 2015), most countries have an influenza vaccination programme (Europe 2019). In Portugal

the influenza vaccine (IV) is recommended for individuals at risk of post-influenza infection complications; to health care providers and caregivers of children with less than 6 months with chronic conditions. Since 2012, it is offered free of charge to individuals aged more 65 or more (DGS 2012). To monitor vaccine coverage, a yearly telephone-based survey has been implemented since 1998 (Machado *et al.* 2017). Results show that, until the 2015/16 season, approximately 50% of the non-institutionalised older adults were vaccinated (Machado *et al.* 2017; Pinto *et al.* 2013), increasing to 61% in the 2017/18 season (Machado *et al.* 2018b). However, this is still below the recommended target (75%).

Previous studies have attempted to identify the main predictors of the influenza vaccine uptake. In 2012, Blank P and colleagues observed that, among different IV strategies, the multidimensional approaches had a higher impact on the increasing IV coverage (Blank *et al.* 2012). Therefore, to better predict and promote IV uptake, the contribution of different dimensions (personal, family, cultural, community and country context) should be taken into account.

Several theoretical frameworks can be adapted to consider multiple dimensional contributions to explaining IV uptake (Nyambe *et al.* 2016). One models adopted only to the influenza pandemic vaccine uptake in 2009 was the Social Ecological Model (SEM). SEM considers 5 levels that can influence the adoption of a given preventive measure: 1) individual, 2) interpersonal, 3) organisational, 4) community and 5) policy. The first level includes all the characteristics, beliefs and attitudes related to the individual - several studies concluded that individual characteristics such as sex (Astray-Mochales *et al.* 2016; Endrich *et al.* 2009; Machado *et al.* 2018a), education (Caille-Brillet *et al.* 2013; Chiatti *et al.* 2011; Endrich *et al.* 2009; Jain *et al.* 2017; Wu *et al.* 2017), health status (de Andres *et al.* 2007; Bohmer *et al.* 2011; Chang *et al.* 2013; Chen *et al.* 2017; Muller and Szucs 2007; Wu *et al.* 2017) were determinant factors for IV uptake.

The second level corresponds to the social influence of family or friends - interpersonal behaviour. Family member/friend recommendations (Ganczak *et al.* 2017; Klett-Tammen *et al.* 2016) and number of household members were identified as relevant to the decision of getting the vaccine (Endrich *et al.* 2009; Jain *et al.* 2017). Also, in a review and meta-analysis, not living alone was an important determinant for individuals aged 60 or more to be vaccinated (Jain *et al.* 2017). Higher income has also been associated with higher IV uptake (Caille-Brillet *et al.* 2013; Jain *et al.* 2017).

The SEM framework (Figure 1) identifies the organisational as the third level, which refers to the activities implemented by institutions and organizations with direct influence on the individual – including recommendation provided at a health care unit. Not only the

recommendation from a general practitioner or other specialist has been identified as an important factor associated with IV uptake, but also the number of visits to a health center or hospital (Bohmer *et al.* 2011; Klett-Tammen *et al.* 2016; Machado *et al.* 2018a; Wu *et al.* 2017).



Figure 1. Social ecologic framework: definition of levels

The fourth level – community - relates to social and cultural aspects of the contexts where individuals live. Some authors have found an association between the town/region size (de Andres *et al.* 2007; Chang *et al.* 2013; Endrich *et al.* 2009; Ganczak *et al.* 2017; Vaux *et al.* 2011), or being born in another country and IV uptake (Astray-Mochales *et al.* 2016; Bohmer *et al.* 2011; Jain *et al.* 2017), which could reflect the influence of this level on the behaviour of the individual.

Finally, the fifth level of SEM reflects the policies that are in place in a given country and that have an indirect impact on the accessibility, awareness, and knowledge of the IV (e.g., free of charge vaccination for individuals aged 60 or 65 years old or the chronic conditions - groups for which the vaccine is recommended).

Although extensive work has been done in relation to specific factors and IV uptake in the older adult population, few studies have focused on framing these factors within a multifactorial model. In addition, the SEM framework was only used in the pandemic vaccine and could be of use in the seasonal vaccine. Focused on the older adults with 65 and more years, this study intends to identify and quantify which SEM levels are associated with the seasonal IV uptake in Portugal.

## Methods

### *Study design and sample*

We used data from the 5<sup>th</sup> National Health Survey (NHS), a population-based cross-sectional study held in 2014 by Statistics Portugal and the Portuguese National Health Institute, integrated part of European Health Interview Survey- wave2.

The 5<sup>th</sup> NHS was designed to be a representative sample (n=18204) of the Portuguese population, based on family households, and was obtained using a multi-stage sampling procedure. Data on several sociodemographic and health-related aspects were collected at the individual level (Instituto Nacional de Estatística and Instituto Nacional de Saúde Dr.Ricardo Jorge 2014), one individual by household. Detailed information is described elsewhere (Instituto Nacional de Estatística 2016). For this study, data were restricted to individuals aged 65 years and older.

### *Outcome variable*

Seasonal influenza vaccine uptake was assessed through the question “*When was the last time you had an influenza vaccine shot?*” (month/year) . An individual was considered as vaccinated, at least once in the previous 2 years, if the answer included the year 2013 or 2014.

### *Levels of the Social Ecological Model*

We conducted a review of studies which focused on factors associated with seasonal IV uptake among the elderly. We searched PubMed for articles published in English from 2010 to May 2017. The search strategy included text words with Boolean operators of keywords in the title, abstract and authors’ keywords. The search terms were: (“influenza vaccine” and “elderly” were combined) and (“association” or “determinants” or “predictors”).

The variables within each SEM level (Table 1) were selected according to 1) the review results, SEM and pandemic vaccine studies (Kumar *et al.* 2012), 3) SEM studies on other health preventive measures (Ohri-Vachaspati *et al.* 2015; Raneri and Wiemann 2007; Vella *et al.* 2014) and 4) inclusion in the NHS questionnaire (Instituto Nacional de Estatística and Instituto Nacional de Saúde Dr.Ricardo Jorge 2014).

### *Statistical analysis*

We conducted descriptive analysis considering all the SEM variables. We estimated IV uptake and corresponding 95% confidence intervals stratified by each of the variables. The association of each variable and the IV uptake was evaluated using design-adjusted Rao–Scott version of Pearson’s chi-square test (Rao and Scott 1984).

For each of 5 SEM levels, separate Poisson regression models adjusted for age were fitted to estimate prevalence ratios (PR) of IV uptake and 95% confidence intervals. In each level, for potentially collinear variables only one variable was kept in the model. Variables with categories with response frequency less than 20 were not included in the model.

To evaluate the statistical significance and marginal contribution of each SEM level to explain IV uptake we used the methods outlined by Ohri-Vachaspi et al (Ohri-Vachaspati *et al.* 2015). In brief, we first fitted a model including all variables from all 5 SEM levels (full model). We then fitted 5 models, each one removing variables from a single SEM-level. Each of these models was compared with the full model using the likelihood ratio test, thus determining the joint statistical significance of variables in each SEM level. Additionally, the marginal contribution of each SEM level was measured by a relative reduction in the magnitude of pseudo R square (Colin Cameron and Windmeijer 1997) based on weighted deviance statistic.

Table 1. Description of the variable within each SEM level, definition and categories

Level/ variable	Definition	categories
<b>Demographic</b>		
Age*	Age at time of the interview	5 years categories: 65-69; 70-74, 75-79, 80-84, and 85+
Sex*	Sex	Male and female
<b>1st level Individual</b>		
Education*	Higher educational level achieved	(ECHID): primary, secondary, and tertiary
Health Status ¶	Self rated health status	3 categories: Very Good/good; Fair, and Bad/very bad
Chronic conditions (nr) ¶	Self reported chronic conditions, Number from a total of 17 conditions	None or one, 2, and 3 or more conditions
Smoking status #	Tobacco consumption	Current smoker, former, and never smoker
Daily activities ¶	Personal and instrumental activities of daily living score	None, moderate, and severe
<b>2 nd lever- Interpersonal</b>		
Marital status*	Marital status	Single, married, widow, and divorced
Household equivalized Income*	Family income	Quintil
Cohabitants*	Number of cohabitants in the household	Alone, one, and 2 or more
<b>3 rd level-organization</b>		
Use of health care services §	GP visit and other MD visits (previous 4 weeks); outpatient and hospitalizations in previous 12 month	None, 1, and >=2 visits
Use of preventive examination§	HTA measure, cholesterol, PSA (for male), mamography (for female), cervical (for female), glicose, colonoscopy (in the previous 12 mo)	Yes and no
<b>4 th level- Community</b>		
Urbanization level of area of residence*		Urban, semi-urban, and rural
Social network #	Extent of social network	One, 1 to 2, 3 to 5, and 6 or more
	Overall perceived social support	Poor, moderate, and strong support
Birthplace*	Place of birth	Portugal, other EU member, and other outside EU
<b>5th level- Policy</b>		
Target CD ¶¶	Has a chronic condition for which the influenza vaccine is recommended	Diabetes, cardiovascular, respiratory, renal, kidney, and cancer condition
* EHIS Wave 2 European Background Variables Module, ¶ EHIS Wave 2 European Health Status Module, § EHIS Wave 2 European Health Care Module, # EHIS Wave 2 European Health Determinants Module, ¶¶ Created based on EHIS Wave 2 European Health Status Module variables		

All analysis was stratified by sex. According to current research, there are health behavioural differences between women and men, not only related with the adoption of health-promoting behaviours but also regarding life-styles (Courtenay 2000; Ek 2015; Liang *et al.* 1999). If we



considered that different policies can be developed to target either women or men, the relevance and impact of the determinants at different levels and between levels may be different according to sex.

All estimates were weighted to account for NHS sample design and to match the distribution of the Portuguese population by geographic region, education level, household size, age group and sex (Instituto Nacional de Estatística 2016). Statistical analysis was run using a *survey* package of R 3.5.1 software and *svy* module of STATA 15.1® software and significance level was set at 5%.

## **Results**

A total of 5669 individuals aged 65 and more years were included in the analysis. The proportion of individuals that were vaccinated at least once in the previous two years was 47.0% (95% CI: 44.9 to 49.0). Men reported an IV uptake of 48.4% (95%CI: 45.4 to 51.5), and women of 45.9% ( 95%CI: 43.4 to 48.6) ( $p = 0.225$ ) (Table 2).

### ***Overall and stratified IV uptake***

#### ***Individual level***

For both sexes, the bivariate analysis revealed a significant increase of the IV uptake with age ( $p < 0.001$ ). A higher IV uptake was found for individuals with bad or very bad self-rated health, among those with 3 or more chronic conditions, never smokers and among those with moderate or severe impairment to perform daily activities (personal or instrumental) (Table 2).

#### ***Interpersonal level***

In either women or men, none of the variables representing the interpersonal level were associated to IV uptake (Table 2).

#### ***Organisational level***

The analysis revealed that men with a medical consultation (both in the primary or hospital setting), or being hospitalised and participating in a preventive screening in the 12 months previous to the survey were factors associated with a higher IV uptake.

Table 2. IV uptake in 2 previous years (%) in the different variables in the SEM levels, stratified by sex

Male					Female			
Variable	n	%	95% CI	p-value	n	%	95% CI	p-value
IV uptake	2202	48.4	[45.4, 51.5]		3467	45.9	[43.4, 48.6]	
<b>Age</b>				<b>&lt;0.001</b>				<b>&lt;0.001</b>
65-69	651	36.4	[31.3, 41.8]		876	34.7	[30.0, 39.7]	
70-74	510	51.7	[45.4, 58.0]		801	44.7	[39.2, 50.2]	
75-79	472	52.8	[46.3, 59.3]		777	50.9	[45.5, 56.3]	
80-84	348	53.3	[46.5, 60.1]		626	51.0	[44.6, 57.3]	
≥85	221	61.8	[52.4, 70.3]		387	55.3	[47.7, 62.7]	
INDIVIDUAL LEVEL								
<b>Education</b>				0.7979				0.0124
Primary	1791	49.0	[45.6, 52.4]		3061	47.5	[44.7, 50.4]	
Secondary	291	47.0	[39.4, 54.8]		247	34.5	[26.8, 43.2]	
Terciary	120	45.4	[33.1, 58.4]		159	40.6	[30.4, 51.6]	
<b>Self rated health status</b>				<b>&lt;0.001</b>				<b>&lt;0.001</b>
Very Good/good	483	41.0	[35.1, 47.2]		406	29.7	[23.5, 36.9]	
Fair	1137	46.0	[41.7, 50.4]		1672	43.9	[40.2, 47.8]	
Bad/very bad	580	60.0	[54.5, 65.2]		1388	53.4	[49.4, 57.4]	
<b>Number of chronic conditions</b>				<b>&lt;0.001</b>				<b>&lt;0.001</b>
None or 1	745	37.3	[32.4, 42.5]		557	31.3	[25.7, 37.6]	
2 CC	384	45.5	[38.1, 53.0]		428	37.6	[30.7, 45.1]	
≥3 CC	1073	56.6	[52.5, 60.6]		2482	50.5	[47.4, 53.7]	
<b>Smoking status</b>				0.0052				0.0070
Current	201	32.3	[23.52, 42.48]		65	27.3	[12.5, 49.5]	
Former s	1143	51.0	[46.6, 55.3]		160	31.5	[21.9, 42.9]	
Never smoker	858	48.6	[43.8, 53.4]		3242	47.3	[44.7, 50.0]	
<b>Personal Daily activities score</b>				0.0012				0.0326
None	1877	46.4	[43.2, 49.8]		2586	44.0	[41.01, 47.0]	
Moderate	190	56.7	[47.4, 65.4]		475	52.3	[45.9, 58.6]	
Severe	135	65.1	[53.5, 75.1]		406	50.5	[43.4, 57.6]	
<b>Home activities score</b>				0.0004				<b>&lt;0.001</b>
None	1543	45.0	[41.4, 48.7]		1124	36.6	[32.4, 41.0]	
Moderate	303	57.7	[49.8, 65.2]		745	47.7	[42.2, 53.3]	
Severe	356	57.7	[50.5, 64.6]		1598	51.7	[47.9, 55.5]	
INTERPERSONAL LEVEL								
<b>Marital status</b>				0.4934				0.0969

Male					Female				
Variable	n	%	95% CI	p-value	n	%	95% CI	p-value	
Single	99	50.2	[34.6, 65.7]	0.3882	244	46.1	[36.4, 56.1]	0.2744	
Married	1631	48.3	[44.9, 51.8]		133	45.8	[41.9, 49.8]		
					5				
Widow	373	51.6	[43.8, 59.3]		172	47.7	[43.9, 51.5]		
					2				
Divorced	99	37.7	[25.0, 52.3]	166	30.4	[21.7, 40.7]	0.8343		
Household equivalized income									
1st quintil	427	47.7	[40.7, 54.8]	931	42.4	[36.9, 48.0]			
2nd quintil	588	51.7	[46.2, 57.1]	941	50.4	[45.8, 55.0]			
3rd quintil	377	52.2	[44.7, 59.5]	791	46.0	[40.8, 51.3]			
4th quintil	452	44.5	[37.9, 51.3]	0.7399	407	46.1	[38.6, 53.9]	0.8343	
5th quintil	358	46.1	[39.4, 53.0]		397	43.4	[36.5, 50.6]		
Cohabitants									
Live alone	544	45.7	[40.3, 51.2]		177	45.2	[42.0, 48.5]		
					2				
With one person	1380	48.8	[45.2, 52.5]	135	46.8	[43.1, 50.4]	0.8343		
				4					
≥2 person	278	48.7	[40.5, 57.0]	341	45.4	[38.1, 52.8]			
ORGANIZATION LEVEL									
GP visits (previous 4 weeks)				<0.001	0.0004				
None	1516	43.4	[39.5, 47.3]	0.0677	218	41.6	[38.4, 44.8]	0.2255	
					4				
One visit	598	59.1	[53.7, 64.4]		110	51.7	[47.1, 56.3]		
					7				
≥2 visits	87	56.2	[42.3, 69.1]		170	57.6	[45.8, 68.6]		
Other MD visits				0.0677					
None	1829	47.1	[43.6, 50.5]	0.0033	284	45.0	[42.2, 47.9]	0.0012	
					5				
One visit	296	56.6	[49.1, 63.8]		493	51.4	[44.6, 58.0]		
					124	43.8	[31.8, 56.5]		
≥2 visits	76	46.7	[33.3, 60.6]						
Outpatient visits				0.0033					
None	1167	44.1	[39.8, 48.5]	0.0104	178	41.3	[37.9, 44.7]	0.5916	
					2				
One visit	357	49.6	[42.2, 57.0]		570	51.5	[45.0, 57.8]		
					108	50.5	[45.8, 55.5]		
≥2 visits	664	55.8	[50.6, 60.9]		1				
Hospitalization				0.0104					
No	1893	46.8	[43.5, 50.1]	<0.001	299	45.7	[43.0, 48.5]	<0.001	
					0				
Yes	308	57.4	[49.9, 64.6]		476	47.6	[41.0, 54.3]		
Preventive screenings in previous 12 mo				<0.001					
Blood pressure									
No	308	26.5	[19.7, 34.7]			21.5	[15.8, 28.7]		
Yes	1894	51.5	[48.2, 54.7]		309	48.6	[45.8, 51.4]		
					9				
Cholesterol				<0.001	0.0001				
No	459	33.6	[27.4, 40.3]		603	33.0	[26.8, 39.9]		

Male					Female				
Variable	n	%	95% CI	p-value	n	%	95% CI	p-value	
Yes	1743	51.8	[48.4, 55.2]	<0.001	2864	48.4	[45.5, 51.2]	<0.001	
<b>Glicose</b>									
No	476	34.34	[28.48, 40.73]	0.0167	6611	32.61	[26.9, 38.89]	0.5086	
Yes	1726	51.75	[48.32, 55.15]			2806	48.74		[45.91, 51.58]
<b>Colonoscopy</b>									
No	2033	47.1	[44.0, 50.2]	0.0072	3266	45.7	[43.0, 48.4]	0.4554	
Yes	169	59.6	[49.6, 68.94]			2012	49.12		[39.4, 58.9]
<b>PSA (male) or mamography (female)</b>									
No	1853	46.0	[42.7, 49.4]		2770	46.5	[43.6, 49.5]		
Yes	349	57.3	[49.9, 64.4]			697	44.2		[38.8, 49.7]
COMMUNITY LEVEL									
<b>Urban/ rural residence</b>				0.1646	<b>0.0023</b>				
Urban	584	47.6	[42.2, 53.1]	0.8451	971	43.6	[39.2, 48.2]	<b>0.0253</b>	
Semi urban	647	44.8	[39.9, 50.0]		1028	41.7	[36.7, 46.9]		
Rural	971	52.2	[47.4, 57.0]		1468	52.8	[49.0, 56.6]		
<b>Extent of social network</b>				0.2572	<b>0.8656</b>				
None	93	55.4	[40.3, 69.6]		100	42.3	[28.4, 57.5]		
1 or 2	959	48.4	[43.6, 53.3]		1597	44.5	[40.7, 48.3]		
3 or 5	806	48.2	[43.5, 52.9]		1244	43.9	[39.8, 48.0]		
≥6	327	48.8	[41.3, 56.3]		513	54.4	[47.6, 61.1]		
<b>Overall perceived social support</b>									
Poor support	1903	49.5	[46.3, 52.8]		3043	46.27	[43.5, 49.1]		
Intermediate support	248	43.1	[34.0, 52.6]		3789	47.69	[40.2, 55.2]		
Strong support	7	65.7	[27.6, 90.6]		66	53.16	[16.1, 87.1]		
POLICY LEVEL									
<b>Target group due to chronic conditions</b>				<0.001	<0.001				
No	1157	41.4	[37.3, 45.7]		1759	40.5	[37.2, 44.0]		
Yes	1045	55.8	[51.7, 59.8]		1708	51.9	[48.1, 55.8]		

CC-chronic conditions; GP- General Practitioner; MD- Medical Doctor

While all the above-mentioned factors related to a medical appointment were associated to a higher IV uptake, no significant association was observed for hospitalizations or adherence to preventive colonoscopy and mammography.

### *Community level*

None of the variables was associated with IV uptake in men, but different results were observed for women. The type of residential community and the extent of the social network were significantly associated to the vaccine uptake. Living in a rural area (IV= 52.8%) and having 6 or more individuals within their social network (IV=54.4%) were the categories with higher IV uptake.

### *Policy level*

For both men and women, belonging to a target group for vaccination, due to a chronic condition for which the IV is recommended, was significantly associated with the IV uptake.

### **SEM level variables associated to IV uptake**

For each level, Table 3 results indicate which variables are independent of age and other SEM level variables associated with IV uptake. For both sexes, older age groups (85 or more; PR=1.59 for men and PR=1.54 for women) were more likely to be vaccinated in one of the last two seasons when compared to younger 65-69 age group.

Within the individual level, having 3 or more chronic conditions (PR=1.39 for men and PR=1.35 for women) was associated with higher IV uptake when compared to those with none or one condition. Among men, former smokers (when compared to current smokers) were more likely to have had an influenza vaccine (PR=1.44).

For women, in addition to the previous variables, those rating their health status as bad or very bad were 1.41 times more likely to have taken the vaccine when compared to women with perceived good health.

For both sexes, the number of GP and outpatient visits in the previous 4 weeks, and having the blood pressure measured in the past twelve months were associated with IV uptake. The community level was only relevant to the women SEM model. Living in a rural area increased the coverage of IV uptake (PR=1.18) when compared to women living in an urban area.

Belonging to the target group of vaccination due to the presence of chronic conditions within the already target group 65 years or more, increased IV uptake in 31% and 23% in men and women, respectively.

### **Contribution of each SEM level to IV uptake**

For men, 2 out of the 5 SEM levels were relevant for explaining IV uptake, namely the individual and organisational level. The organisational level was the one that had the main impact on the final model (Table 4). Different results were observed for women, where 3 levels were significant in explaining IV uptake. For women, in addition to the identified levels

(individual and organisational), the community (type of residence area) was also significant in the final model.

Table 3. Multivariate analysis within SEM levels

Variable	PR	Male 95% CI	p-value	PR	Female 95% CI	p-value
<b>Age group</b> (REF= 65-69 years)						
70-74	1.37	[1.14 - 1.64]	0.001	1.22	[1.01 - 1.46]	0.039
75-79	1.35	[1.12 - 1.63]	0.001	1.37	[1.15 - 1.63]	0.000
80-84	1.40	[1.15 - 1.7]	0.001	1.34	[1.1 - 1.62]	0.003
≥85	1.59	[1.3 - 1.96]	0.000	1.54	[1.26 - 1.89]	0.000
<b>Individual level</b>						
<b>Education</b> (REF= Primary)						
Secondary	1.10	[0.92 - 1.31]	0.292	0.98	[0.76 - 1.26]	0.865
Tertiary	1.12	[0.86 - 1.45]	0.390	1.22	[0.92 - 1.61]	0.161
<b>Self rated health status</b> (REF= Very Good/good)						
Fair	1.03	[0.86 - 1.22]	0.760	1.26	[0.98 - 1.62]	0.071
Bad/very bad	1.19	[0.98 - 1.46]	0.086	1.41	[1.08 - 1.83]	0.012
<b>Number of chronic conditions</b> (REF= None or 1)						
2 CC	1.18	[0.96 - 1.45]	0.111	1.08	[0.83 - 1.42]	0.557
≥3 CC	1.39	[1.19 - 1.63]	0.000	1.35	[1.09 - 1.68]	0.006
<b>Smoking status</b> (REF= Current)						
Former smoker	1.44	[1.07 - 1.93]	0.016	1.04	[0.48 - 2.27]	0.919
Never smoker	1.33	[0.98 - 1.8]	0.064	1.40	[0.69 - 2.81]	0.349
<b>Personal Daily activities score</b> (REF= None)						
Moderate	0.97	[0.78 - 1.21]	0.797	1.00	[0.86 - 1.15]	0.949
Severe	1.20	[0.93 - 1.55]	0.152	0.87	[0.73 - 1.05]	0.140
<b>Home activities</b> (REF= None)						
Moderate	1.08	[0.89 - 1.32]	0.427	1.13	[0.95 - 1.33]	0.160
Severe	0.92	[0.74 - 1.14]	0.436	1.11	[0.95 - 1.31]	0.194
<b>Interpersonal level</b>						
<b>Marital status</b> (REF= Single)						
Married	1.02	[0.73 - 1.42]	0.930	1.09	[0.86 - 1.37]	0.480
Widow	0.96	[0.67 - 1.38]	0.824	1.01	[0.81 - 1.26]	0.920
Divorced	0.84	[0.52 - 1.34]	0.464	0.77	[0.53 - 1.11]	0.161
<b>Household equivalized income</b> (REF= 1st quintil)						
2nd quintil	1.05	[0.88 - 1.26]	0.565	1.21	[1.04 - 1.41]	0.012
3rd quintil	1.10	[0.9 - 1.35]	0.334	1.11	[0.94 - 1.32]	0.210
4th quintil	0.95	[0.77 - 1.17]	0.615	1.13	[0.9 - 1.41]	0.285
5th quintil	1.00	[0.82 - 1.22]	0.995	1.09	[0.89 - 1.35]	0.406
<b>Organization level</b>						
<b>GP visits (previous 4 weeks)</b> (REF= None)						
One visit	1.25	[1.1 - 1.42]	0.001	1.13	[1.01 - 1.28]	0.039
≥2 visits	1.06	[0.8 - 1.42]	0.677	1.27	[1.02 - 1.59]	0.035
<b>Other MD visits</b> (REF= None)						
One visit	1.05	[0.89 - 1.22]	0.584	1.05	[0.91 - 1.21]	0.522
≥2 visits	0.77	[0.57 - 1.06]	0.108	0.89	[0.66 - 1.19]	0.426
<b>Outpatient visits</b> (REF= None)						

Variable	Male			Female		
	PR	95% CI	p-value	PR	95% CI	p-value
One visit	1.02	[0.86 - 1.21]	0.837	1.16	[1 - 1.35]	0.049
≥2 visits	1.12	[0.99 - 1.28]	0.077	1.10	[0.97 - 1.24]	0.123
Preventive screenings in previous 12 mo (REF= No)						
HTA measure	1.56	[1.14 - 2.14]	0.005	1.90	[1.36 - 2.65]	0.000
Cholesterol	1.19	[0.96 - 1.46]	0.112	1.08	[0.87 - 1.34]	0.499
Colonoscopy	1.18	[0.99 - 1.4]	0.069	1.04	[0.85 - 1.28]	0.677
<b>Community level</b>						
Urban/ rural residence (REF= Urban)						
Semi urban	0.92	[0.79 - 1.08]	0.335	0.94	[0.81 - 1.11]	0.481
Rural	1.05	[0.91 - 1.21]	0.497	1.18	[1.05 - 1.34]	0.008
Extent of social network (REF= None)						
1 or 2	0.89	[0.67 - 1.19]	0.434	1.03	[0.72 - 1.47]	0.860
3 or 5	0.90	[0.67 - 1.21]	0.489	1.02	[0.72 - 1.46]	0.900
≥6	0.89	[0.65 - 1.22]	0.457	1.26	[0.87 - 1.83]	0.211
<b>Policy level</b>						
Target group due to Chronic conditions (REF= No)						
Yes	1.31	[1.17 - 1.48]	0.000	1.23	[1.1 - 1.38]	0.000

CC-chronic conditions; GP- General Practitioner; MD- Medical Doctor

Table 4. Multivariate analysis all SEM levels

Male				Female		
	PR	IC95%	p-value	PR	IC95%	p-value
<b>FullModel</b> AIC=1453.7 R(Dev)= 0.0863				AIC= 2338.99 R(Dev)= 0.07876		
Age group (REF= 65 – 69 years)				(REF= 65 – 69 years)		
70-74	1.38	[1.15 - 1.65]	0.000	1.18	[0.99 - 1.41]	0.067
75-79	1.38	[1.15 - 1.66]	0.001	1.35	[1.14 - 1.6]	0.001
80-84	1.42	[1.17 - 1.72]	0.000	1.34	[1.11 - 1.62]	0.002
≥85	1.63	[1.31 - 2.02]	0.000	1.59	[1.31 - 1.94]	0.000
<b>Individual level</b> AIC= 1458.3 R(Dev)= 0.0704, MC= 18.4% LTR= 26.95, p-value= 0.0103 Statistically significant				AIC= 2340.97 R(Dev)= 0.065626, MC= 10.6% LTR= 23.92, p-value= 0.030383 Statistically significant		
Education (REF= Primary)				(REF= Primary)		
Secondary	1.08	[0.89 - 1.32]	0.416	0.90	[0.69 - 1.17]	0.410
Tertiary	1.18	[0.88 - 1.57]	0.262	1.07	[0.78 - 1.48]	0.667
Self rated health status (REF= Very Good/good)				(REF= Very Good/good)		
Fair	1.03	[0.87 - 1.21]	0.757	1.23	[0.97 - 1.55]	0.086
Bad/very bad	1.15	[0.95 - 1.4]	0.144	1.33	[1.03 - 1.71]	0.028
Number of chronic conditions (REF= None or 1)				(REF= None or 1)		
2 CC	1.07	[0.87 - 1.32]	0.519	1.00	[0.78 - 1.29]	0.975
≥3 CC	1.24	[1.04 - 1.49]	0.019	1.18	[0.96 - 1.45]	0.121
Smoking status (REF= Current)				(REF= Current)		
Former smoker	1.45	[1.08 - 1.95]	0.014	1.32	[0.5 - 3.48]	0.573
Never smoker	1.35	[0.99 - 1.83]	0.058	1.68	[0.68 - 4.15]	0.260
Personal Daily activities score (REF= None)				(REF= None)		
Moderate	0.98	[0.78 - 1.22]	0.831	0.99	[0.86 - 1.15]	0.945

Severe	1.18	[0.91 - 1.55]	0.215	0.89	[0.74 - 1.06]	0.198
Home activities						
None	REF			REF		
Moderate	1.10	[0.89 - 1.35]	0.387	1.11	[0.95 - 1.3]	0.196
Severe	0.91	[0.73 - 1.14]	0.427	1.06	[0.9 - 1.25]	0.481
<b>Interpersonal level</b> AIC= 1446.3 R(Dev)= 0.08399, , MC= 2.7% LTR= 4.39, p-value= 0.72817 not significant				AIC= 2337.2 R(Dev)= 0.07347, MC= 6.7% LTR= 11.82, p-value=0.110 not significant		
Marital status (REF= Single)				(REF= Single)		
married	0.97	[0.7 - 1.33]	0.836	1.06	[0.84 - 1.34]	0.626
widow	0.98	[0.69 - 1.39]	0.899	0.98	[0.78 - 1.23]	0.866
divorced	0.80	[0.5 - 1.27]	0.341	0.84	[0.58 - 1.21]	0.346
Household income (REF= 1st quintile)				(REF= 1st quintile)		
2nd quintil	1.00	[0.84 - 1.18]	0.972	1.17	[1 - 1.35]	0.045
3rd quintil	1.13	[0.92 - 1.38]	0.234	1.14	[0.96 - 1.34]	0.126
4th quintil	0.97	[0.78 - 1.2]	0.760	1.20	[0.97 - 1.47]	0.096
5th quintil	0.97	[0.77 - 1.22]	0.802	1.29	[1 - 1.66]	0.051
<b>Organization level</b> AIC= 1480.4 R(Dev)= 0.059, , MC= 31.3% LTR= 46.71, p-value<0.001 Statistically significant				AIC= 2364.3 R(Dev)= 0.060, MC= 23.2% LTR= 37.67, p-value<0.001 Statistically significant		
GP visits (previous 4 weeks) Ref (None)				Ref (None)		
One visit	1.25	[1.1 - 1.41]	0.001	1.08	[0.96 - 1.21]	0.202
≥2 visits	0.99	[0.76 - 1.3]	0.962	1.17	[0.95 - 1.46]	0.143
Other MD visits Ref (None)				Ref (None)		
None	REF			REF		
One visit	1.00	[0.86 - 1.17]	0.962	1.04	[0.9 - 1.2]	0.579
≥2 visits	0.80	[0.6 - 1.07]	0.134	0.92	[0.69 - 1.22]	0.541
Outpatient visits Ref (None)				Ref (None)		
None	REF			REF		
One visit	1.00	[0.84 - 1.18]	0.954	1.14	[0.99 - 1.32]	0.059
≥2 visits	1.05	[0.92 - 1.19]	0.491	1.04	[0.93 - 1.18]	0.485
Preventive screenings in previous 12 mo Ref (No)				(REF= No)		
HTA measure	1.41	[1.03 - 1.93]	0.031	1.86	[1.35 - 2.55]	0.000
Cholesterol	1.23	[1 - 1.51]	0.054	1.01	[0.83 - 1.22]	0.940
Colonoscopy	1.12	[0.94 - 1.33]	0.220	1.02	[0.83 - 1.26]	0.829
<b>Community level</b> AIC= 1447.3 R(Dev)= 0.08488, , MC= 1.7% LTR= 2.54, p-value = p= 0.76775 not significant				AIC= 2352.1 R(Dev)= 0.069592, MC= 11.6% LTR= 19.96, p-value= 0.00155 Statistically significant		
Urban/ rural residence (REF= Urban)				(REF= Urban)		
Urban	REF			REF		
Semi urban	0.90	[0.77 - 1.05]	0.192	0.91	[0.78 - 1.06]	0.224
Rural	0.98	[0.85 - 1.13]	0.783	1.15	[1.02 - 1.3]	0.027
Extent of social network (REF= None)				(REF= None)		
None	REF			REF		
1 or 2	0.91	[0.69 - 1.2]	0.514	1.02	[0.72 - 1.46]	0.897
3 or 5	0.91	[0.68 - 1.2]	0.490	1.00	[0.7 - 1.43]	0.982
≥6	0.91	[0.67 - 1.24]	0.549	1.23	[0.85 - 1.76]	0.268
<b>Policy level</b> AIC=1452.6 R(Dev)= 0.086, MC= 0.7% LTR= 0.87, p-value= 0.352				AIC= 2338.5 R(Dev)= 0.078, , MC= 0.8% LTR= 1.54, p-value= 0.216		



not significant				not significant		
Target group due to	(REF= No)			(REF=No)		
Chronic conditions						
Yes	1.07	[0.93 - 1.23]	0.351	1.07	[0.96 - 1.2]	0.214

LTR: likelihood ratio test statistics

MC: marginal contribution (%)=  $[R(Dev)_{Full\ model} - R(Dev)_{Full\ model-SEM\ level}] / R(Dev)_{Full\ model} \times 100$

## Discussion

As prior hypothesised, our results indicate that different levels of the social ecological model are associated to IV uptake in the non-institutionalised Portuguese population aged 65 and more, and the results are different in men and women. For both sexes, within the individual level, the results highlight that having 3 or more chronic conditions were associated with higher IV uptake. For men, the smoking status and for women self-rated health status were also significantly associated with the IV uptake. This set of variables was already identified in previous studies (Astray-Mochales *et al.* 2016; Bohmer *et al.* 2011; Chen *et al.* 2017; Wu *et al.* 2017) as associated with seasonal IV uptake in the population aged 65 and more, even though the results are not stratified by sex.

The interpersonal level was only significantly associated with IV uptake for women, but after adjustment for all variables, this level was not relevant (p-value=0.1103). Other studies have not found income (Chiatti *et al.* 2011), marital status (Machado *et al.* 2018a) or cohabitants (Vaux *et al.* 2011) to be associated with IV uptake. The results may be related with this specific group of the population that has, since 2012, access to free of charge vaccine, which may reduce any income-related inequalities.

In line with several other studies (Bohmer *et al.* 2011; Klett-Tammen *et al.* 2016; Machado *et al.* 2018a; Wu *et al.* 2017), the use of health care services was significantly associated with the IV uptake. The measurement of blood pressure in the previous 12 months was also associated with the vaccine uptake, in addition to 1 GP visit in the previous 4 weeks for men. This result emphasises the importance to take advantage of the patient contact to the primary care setting. On one hand, the opportunity for the IV uptake is higher among those that use more frequently the health care services, hence more prone to be identified by the services. It would be important to explore this result in order to fully understand which can be attributed to the individual behaviour and the organisational level. The community level was only relevant to the women's SEM model. According to our results, living in a rural area increased the IV uptake in 21% when compared to women that lived in an urban area. These results are in accordance with other studies (Endrich *et al.* 2009).

Finally, the policy level was significantly associated to the IV uptake for both women and men, and belonging to the target group of vaccination due to the presence of certain chronic conditions, increased IV uptake in 31% (men) and 23% (women). These individuals belong to the target group due to dual criteria, because of their age (65 years or more) and also because of a health condition that increases the risk of post-infection complications. However, after adjustment this level was not significant in either SEM models. This may be due to the high collinearity with previous levels (particularly the individual level and the health condition variable) and the policy considered at this level.

To our knowledge, this is the first study that stratifies the analysis considering the gender, and thus the comparison with other studies is limited. Differences seem to be related to smoking status for men and self-rated health status, household equalised income and rural residence for women. Nevertheless, more similarities than differences were observed between men and women. Some evidence indicates that differences between the sexes regarding health-seeking behaviour, lifestyles and use of health care (23–25) do not remain the same over the life span - the gap seems to decrease with increased age (Liang *et al.* 1999) or increased health-related issue seriousness (Galdas *et al.* 2005). Also, it has been suggested that gender might be carrier variable or confounder of explanatory factors rather than explanatory factor by itself (Doherty *et al.* 2016), given that it can be related with other determinants.

Similarly, the final model shows that individual and organisational levels contributed to explaining IV uptake for both sexes; for women, the community level also had some contribution. Our results differ from Kumar *et al.* (Kumar *et al.* 2012), who applied the SEM to study influenza pandemic vaccine uptake. In their study, all the levels significantly contributed to the influenza pandemic vaccine uptake in 2009/10. The reason for this difference might be two-fold. Firstly, the vaccine under study (pandemic influenza). Secondly, the target group, as the monovalent influenza vaccine was recommended to older as well as to younger individuals while seasonal vaccine targets the ones aged 65 years and more and individuals with chronic conditions. A review identifying predictors of seasonal and pandemic influenza vaccination for risk groups and the general public has shown differences between determinants in each of the groups (Schmid *et al.* 2017). For instance, among chronically ill patients, while smoking status was found to be a predictor for seasonal influenza vaccine uptake, the same was not observed for pandemic influenza. In addition, factors influencing vaccination uptake seem to be context specific (Butler *et al.* 2015). In Portugal, for the risk groups targeted for the vaccine, individual and organisational may be more relevant than other levels, particularly the organisational level. In the final model, the organisational level was responsible for the marginal variation in model explanation of 31.3% (men) and 23.2% (women), the individual level for the marginal variation of 18.4% (men) and 10.6% (women) and for women the community level was responsible for the marginal variation of 11.6%.

These results show that not all levels may contribute equally for IV uptake and that regardless of the differences, the organisational level seems to be the most relevant. Despite the existing evidence of individual level in IV uptake, this may not explain entirely the actual phenomenon as individual level may be regulated by other levels.

There are limitations to be accounted for. First, the cross-sectional nature of the study and, second, the time frame to which several variables are related. The focus of the analysis was the NHS conducted in 2014, where the main outcome (vaccine uptake) was recorded up to 2 previous years. The results reflect association of several independent variables measured at different time frames to IV uptake, not a causal relation; therefore the prevalence ratio should be interpreted accordingly. The conceptual SEM model was designed based on the variables available on the NHS, which does not include all relevant variables. This could have an impact on the SEM level contribution to the overall model. The levels that contributed more to the full model were also the ones with more variables. Second, it was not possible to assess perception and awareness to IV uptake (Kumar *et al.* 2012). Despite the variability of beliefs and attitudes towards health behaviours and vaccination, in particular, studies show that there are similarities among subgroups of the population according to sociodemographic characteristics (Galdas *et al.* 2005; Liang *et al.* 1999; Santos *et al.* 2017). Therefore, the absence of this information should not have introduced an important source of bias, as they were captured by the sociodemographic variables included in the study.

Our results were obtained using survey data, designed to be representative of the population, with a high participation rate (80.8%) (Instituto Nacional de Estatística and Instituto Nacional de Saúde Dr. Ricardo Jorge 2014). Within the limitations previously discussed, the weighted results reflect the prevalence and association of the SEM levels with IV uptake in the Portuguese population aged 65 and more. Considering that NHS is a harmonised population-based survey that is applied routinely it could be used to monitor and compare along with the years' changes that could be important to adjust the IV strategy. Finally, the variables identified for this study allow us to identify groups less likely to be vaccinated which should be a target in future interventions.

As such, these results can be used to strength IV uptake interventions with a particular focus on the levels with higher relevance in this preventive behaviour for both sexes, i.e., organisational and individual level. Interventions at organisational level should be tailored to promote systematic recommendation of the vaccine (Kolff *et al.* 2018). Following the results of a study using SEM framework (Kolff *et al.* 2018), the individual factors could be targeted to minimise missed opportunities to recommend the vaccine. The importance of the primary health care setting and the contact with individuals also highlights the importance of recommendation and promoting campaigns at this level. Also, it is important to find alternative strategies to contact with healthier individuals and smoker, with lower contact with the health care, that will miss interventions at health care.

On the other hand, and particularly for women, the community could play an important role. At community level (Kolff *et al.* 2018), it has been suggested that the use of recalls (for instance text messages reminders) could be used as effective interventions. Also, the intensification of communication at local level through pamphlets, flyers and radio (Thomas and Lorenzetti 2018) could result in higher IV uptake. Other studies suggested these messages to focus both on the disease burden and the role of IV in the prevention of influenza and related

complications (Kolff *et al.* 2018; Santos *et al.* 2017). Strategies developed in an urban area could also be different from an urban one.

## Conclusions

In a complex and multidimensional preventive behaviour, as influenza vaccine uptake, the SEM framework was successful in identifying the individual and organisational level as main contributors to explain the influenza vaccine uptake in the older adult Portuguese population. For women, the model also added the community level and highlighted the importance of the residency area.

For both sexes, the contact with primary care units was key in the seasonal influenza vaccine uptake. This result highlights the need to better understand the relationship between actively seeking and using health care centers and the opportunity for vaccination.

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## 5.2 Influenza vaccine effectiveness

The research question *"What is the vaccine effectiveness in reducing the influenza disease and its related complications?"* was addressed in two studies, developed in two different settings.

Within study 3, *"Is there effect modification of influenza vaccine effectiveness by age and chronic conditions?"*, besides measuring IVE against medically attended influenza in primary care, it also looked into the potential effect modification of older age and presence of chronic conditions.

Study 4, *"Implementing an influenza vaccine effectiveness against hospitalized influenza study in Portugal"*, describes the implementation, challenges and added value of EVA Hospital project in Portugal. At national level, this is the first IVE study that looks into severe influenza and the older adult population.



## Is there effect modification of influenza vaccine effectiveness by age and chronic conditions?

Running title: Age and chronic condition as IVE effect modifiers

Ausenda Machado<sup>1,2</sup>, Andreia Leite<sup>2,3</sup>, Amparo Larrauri<sup>4</sup>, Verónica Gomez<sup>1</sup>, Ana Paula Rodrigues<sup>1</sup>, Irina Kislaya<sup>1,2</sup>, Baltazar Nunes<sup>1,2</sup>

1 – Departamento de Epidemiologia, Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa, Portugal

2 - NOVA National School of Public Health, Public Health Research Centre, Universidade NOVA de Lisboa, Lisbon, Portugal

3 - Unidade de Saúde Pública, Agrupamento de Centros de Saúde Amadora, Portugal

4 - National Centre of Epidemiology, Institute of Health Carlos III. CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

### Abstract

Most European influenza vaccine strategies target high-risk individuals that have both high-risk of post-infection complications and lower capacity of acquiring adequate vaccine-induced protection. Some chronic conditions and age have been described as potential confounders of influenza vaccine effectiveness, but instead they could modify the effect of vaccine.

Based on 8 seasons of a test-negative design, this study aimed at assessing the potential effect modification of influenza vaccine effectiveness (IVE) by age and chronic conditions. Influenza vaccine effectiveness (IVE) was estimated as 1 – Odds Ratio (OR) of being vaccinated in cases versus controls. OR was obtained using multivariable conditional logistic regression model, paired by week of onset within each season, to control for confounding. Confounders were assessed by designing a specific causal diagram. Age and chronic conditions were studied as effect modifiers by including an interaction term in the regression models. Significance was established in 5%.

Point estimates indicate a higher IVE in the chronic condition strata than in the no chronic condition ones. Regarding age, different results were obtained considering the virus type and (sub)type. When comparing the 65 and more years of age strata with the <65 years strata we observed higher IVE against A(H1N1)pdm09, equal IVE against A(H3N2) and lower IVE against B virus. All interactions terms were however not statistically significant and this may be due to small sample size.

The potential effect modification of age or chronic condition was not observed within our study. Given the subject matter, further studies with larger sample sizes are required.

**key words:** influenza vaccine, effectiveness, age, chronic condition, effect modification

## Introduction

In Portugal, as in most European countries, seasonal influenza vaccine (IV) is recommended to high-risk individuals on a yearly basis (1,2). High-risk individuals are those more prone to post-influenza infection complications, including older adults aged 65 years and more and individuals with chronic conditions (3). The risk based strategy is thus intended to prevent the infection and reduce associated complications, such as hospital admissions and hospitalizations in intensive care (3).

Yearly monitoring of influenza vaccine effectiveness demonstrate that available vaccines confer low to moderate protection against seasonal influenza (4,5). In some seasons, influenza vaccine effectiveness (IVE) has been particularly low in the 65 and more years population (6–8). There are some host specific factors that may compromise the individual ability to produce adequate antibodies after vaccination, namely, age and correspondent age-related comorbidities, genetic polymorphism and chronic immunocompromised conditions (9).

In the 2016/17 season, Stein et al. (10) studied the relationship of influenza vaccine effectiveness and age using the test-negative design, and observed a decline of the vaccine protection with increasing age. Although previous study on United States found no statistical evidence of a difference between IVE on younger and older adults (11), immunosenescence and past history of exposure to the influenza or to the vaccine could be related with a decreased immune response to vaccine exposure on older adults (12,13).

Additionally, existing conditions may impact vaccine-induced immune response. This includes both immunocompromising conditions and chronic conditions which increase the risk of influenza complications (14,15). Looking to specific chronic conditions, the reduced immunocompetence of immunosuppressed individuals (under cancer treatment or HIV) (9), may impair individuals capability to achieve adequate antibodies titers. Another chronic conditions with high risk of influenza complications and potential lower IVE, is diabetes. A systematic review and meta-analysis on patients aged 18-64 years with diabetes, estimated that the influenza vaccine was 58% (IC95%: 6 a 81%) against all hospitalizations and 43% (IC95%: 28 a 54%) for pneumonia and influenza hospitalizations. Once again, authors stated the need for more studies with quality to robust these results (14). Moreover, there is some evidence that some chronic condition medication may interfere with the individual capacity to produce vaccine-induced antibodies (16–18). For instance, statin users have been described to have a weaker response to the influenza vaccine than non-users in hospitalized individuals (19).

All the above considered, the traditional influenza vaccination strategy might be targeting individuals that, although at high-risk of influenza complications, may have lower capacity of acquiring adequate

vaccine-induced protection. This could have consequences on the recommendations for complementary preventive strategies, namely antivirals, and on vaccination schedule. It could also add to the discussion on targeting alternative groups (20).

This study aimed at assessing age and chronic conditions as potential effect modifiers of influenza vaccine effectiveness, what might add to the discussion on a possible change in the vaccination recommendations.

## **Methods**

### *Study design*

We used the test-negative design, where laboratory confirmed RT-PCR influenza cases were compared to tested negative controls.

### *Data collection and setting*

We used data from 2010/11 to 2017/18 seasons. Data were retrieved from EuroEVA study (21), the Portuguese component of the multicentric primary care based study of I-MOVE network (Influenza - Monitoring Vaccine Effectiveness) (22). Detailed information on recruitment can be found elsewhere (21,22). In short, patients with influenza like-illness symptoms (ILI), according to the European criteria (23) were recruited during a general practitioner (GP) consultation. After written consent, a swab was collected for laboratory analysis. Epidemiological and clinical data including vaccination status and date of vaccination was gathered using a standardized form.

### *Variables*

Main exposure was seasonal influenza vaccine uptake. An individual was considered as vaccinated if inoculation with trivalent inactivated vaccine occurred 14 days before symptoms onset.

The outcome was RT-PCR influenza positive, any and specific (sub)-types A(H1N1)pdm09, A(H3N2) and B.

A set of potential confounders were collected, including sociodemographic (age, sex, education, number of cohabitants); health status (chronic conditions, requires assistance to bath, hospitalizations); use of health care (number of visits to a GP) and health behavior (tobacco consumption) variables.

The list of chronic conditions collected within the study, and for which the seasonal influenza vaccine is recommended, included: diabetes, cardiovascular disease (congenital heart disease, hypertensive heart disease, ischaemic heart disease, chronic heart failure), chronic renal disease (chronic renal

failure and nephrotic syndrome), chronic hepatic disease (cirrhosis, billiar atresia and chronic hepatitis), obesity (body mass index $\geq 30$ ), chronic respiratory disease (asthma, chronic bronchitis, emphysema, bronchopulmonary dysplasia, cystic fibrosis, pneumoconiosis and pulmonary fibrosis), congenital or acquired immunodeficiency (conditions that suppress the immune function due to underlying disease and/or therapy, e.g. chemotherapy, HIV infection) and neuromuscular disease.

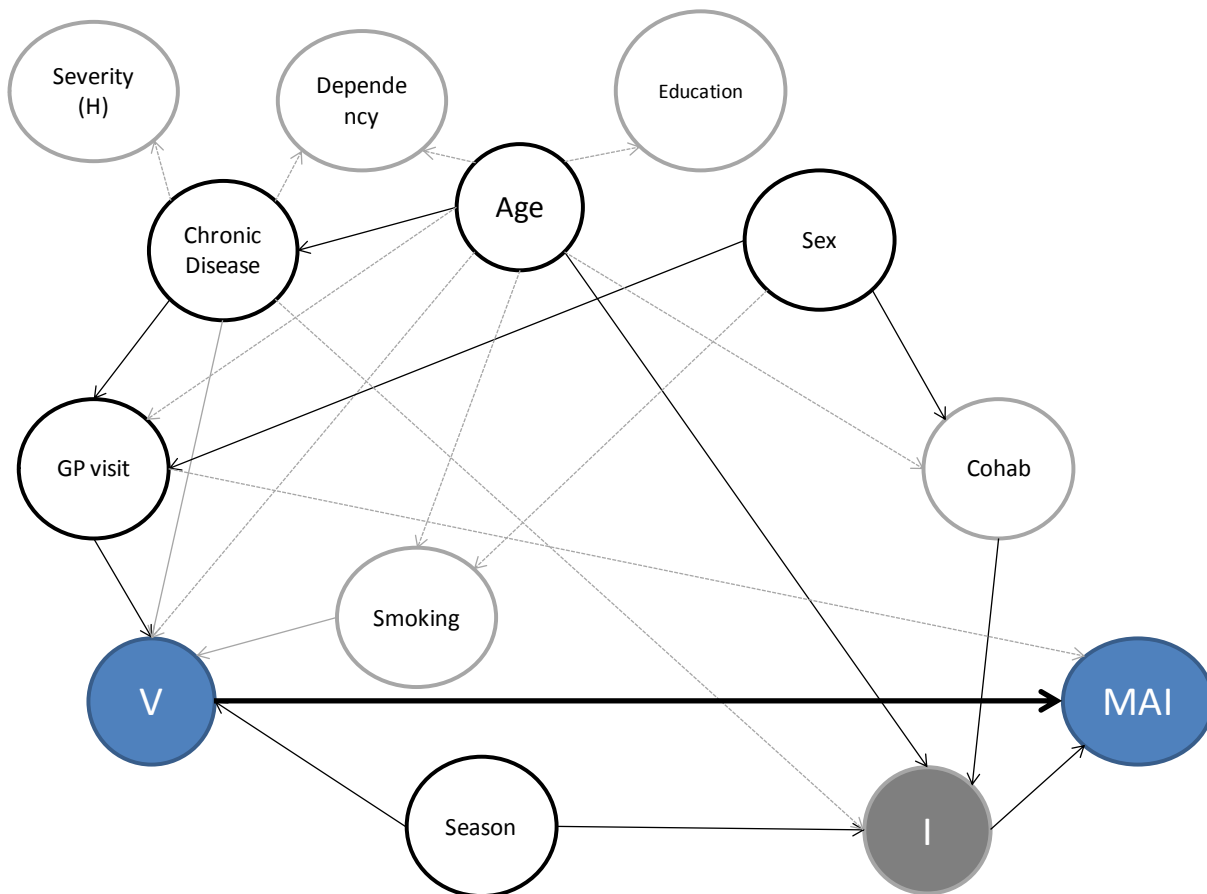
An individual was considered as having a chronic condition if at least one of the previous conditions was recorded in his/her medical record. Age was categorized as a binary variable (<65 years and  $\geq 65$  years).

### Statistical analysis

Study participants were described according to baseline characteristics. Baseline characteristics of cases (any influenza and specific subtypes) and controls were compared using the Chi-square test or the Fisher's exact test.

Influenza vaccine effectiveness (IVE) was estimated as  $1 - \text{Odds Ratio (OR)}$  of being vaccinated in cases versus controls. Exact 95% confidence intervals were computed around the point estimates. OR was obtained using multivariable conditional logistic regression model, paired by week of onset within each season, to control for confounding.

A theoretical model of the causal relation between influenza vaccination and medically attended influenza was built using a directed acyclic graph (DAG) (24). Starting from the set of variables collected within the project, the connections within the DAG were established considering previous Portuguese studies on influenza vaccine associated factors (25,26) and meta-analysis of influenza risk factors (27). These results allowed to identify independent factor to vaccine and influenza, which were connected, assuming a direct effect of the variable on exposure or influenza using DAGITTY (28). The minimum set of variables needed to adjust for confounding was identified using the back-door method (28) and included age, chronic condition, sex, number of GP visits in the previous year and the season (Figure 1).



Legend: V= vaccine; I- Influenza; MAI-Medically attended influenza

Figure 1. Directed Acyclic graph for confounding identification for influenza vaccine effectiveness studies in Portugal

Age and chronic conditions were studied as effect modifiers by including an interaction term in the regression models. Two different models were used, assessing effect modification separately for each effect modifier (age and chronic conditions). In the chronic condition effect modification model, age was introduced in the model using a restricted cubic spline with 4 knots (29).

We report the interaction term of the model (IOR) that measures the ratio between the OR of influenza vaccination among those individuals with the potential effect modifier present (65+ or any chronic disease) versus the OR among those with the effect modifier absent (<65 or no chronic conditions). An IOR>1 means that the OR among those with  $\geq 65$  (or any chronic disease) is higher than the OR among those with <65 years of age (or no chronic disease). This would mean that, for e.g., having more than 65 years of age (having at least one chronic condition) reduces the effect of the influenza vaccine. Otherwise, if IOR<1 means that being 65 plus (or having chronic conditions) increases the effect of the influenza vaccine.

Power to detect an interaction between main exposure (vaccine) and potential effect modifier (age and chronic conditions) were estimated for a range of interaction terms in the OR scale (IOR) from 0.1 (i.e. IV odds ratio in the  $\geq 65$ /any chronic disease of 0.1 the IV odds ratio in the  $< 65$ /no chronic disease) to 3 (i.e. IV odds ratio in the  $\geq 65$ /any chronic disease of 3-fold the IV odds ratio in the  $< 65$ /no chronic disease) based on the work of Vanderweele (30). Power curves were represented graphically for any and specific influenza (sub)types.

#### Ethical issues

EuroEVA study was submitted and approved by the Ethical Committee of the National Health Institute Ricardo Jorge. The study protocol was also authorized by the National Committee for Data Protection (*Comissão Nacional de Proteção dos Dados, authorization nr. 6082/2015*). Participants were included only after written informed consent. The study was conducted following research standards of Declaration of Helsinki.

#### Results

From season 2010/11 to 2017/18 a total of 2451 ILI patients were recruited. Analysis was restricted to patients that had ILI according to the defined criteria and for whom a swab was collected within 7 days of symptom onset ( $n=2285$ ). According to laboratory results, 1085 were positive for an influenza virus (cases) and 1200 were negative controls. Among cases, 336 were positive for subtype A(H1)pdm09; 404 for subtype A(H3) and 345 for type B (87 B/Victoria and 258 B/Yamagata). Subtype A(H1)pdm09 virus was more frequently detected in seasons 2010/11, 2012/13 and 2015/16 and A(H3) virus in seasons 2011/12 and 2016/17 (Figure 2). Type B virus was detected simultaneously with A(H1)pdm09 in seasons 2010/11, 2012/13 and also in seasons 2014/15 and 2017/18.



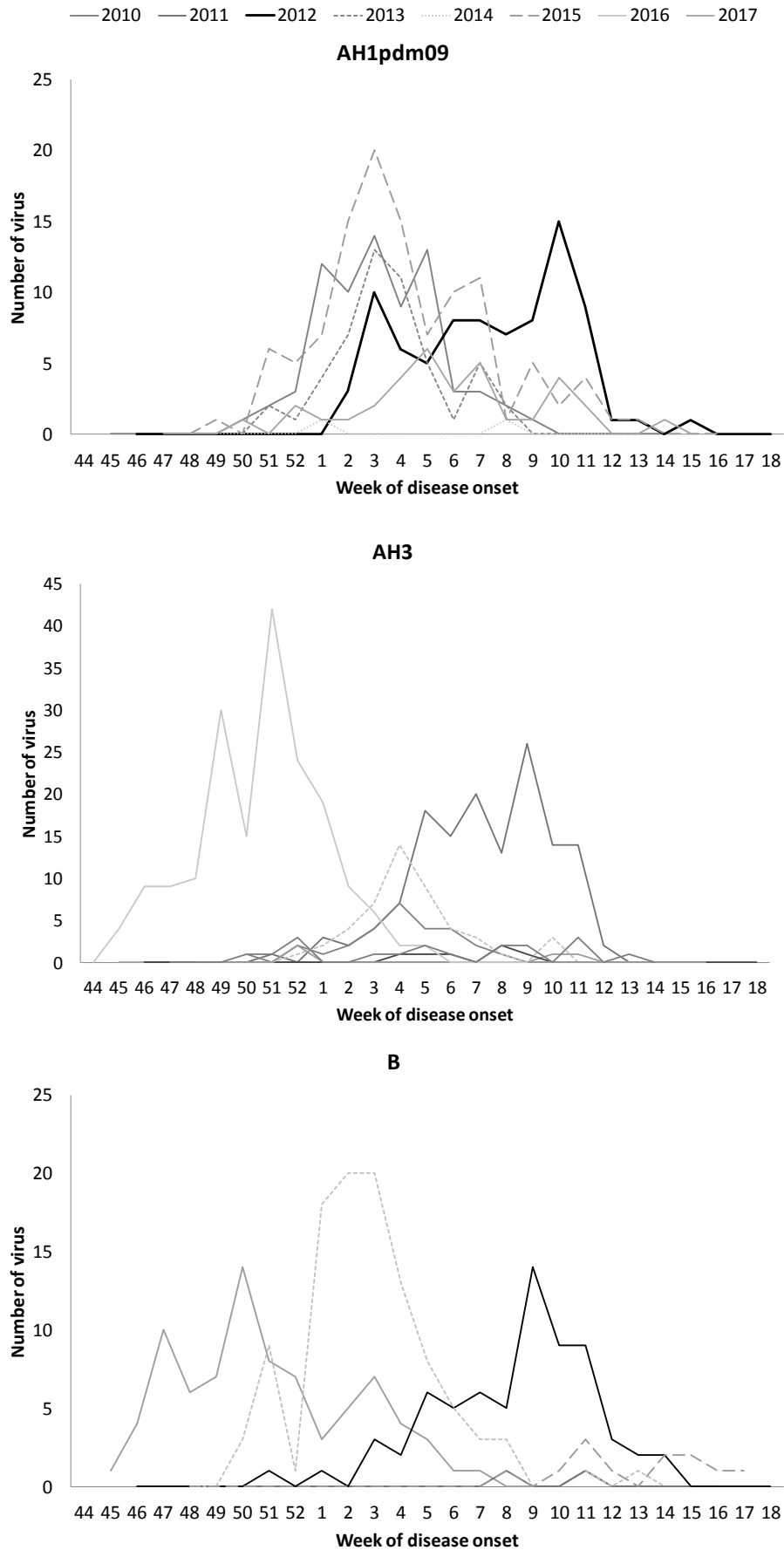


Figure 2. Weekly (ISO weeks) distribution of influenza cases; seasons 2010/11 to 2017/18

There was evidence of a difference between any influenza and specific (sub)types cases and controls regarding age (cases were younger than controls), presence of chronic conditions (higher frequencies in controls) and GP visits and hospitalizations (more frequent in controls) (Table 1). Regarding ILI signs and symptoms, cases reported more frequently fever, malaise and cough, independently of the virus (sub)type.

Adjusted IVE was 51.8% [95%CI: 34.8-64.3] against any influenza (Table 2). A similar estimate was obtained against A(H1N1)pdm09 (IVE= 50.9%; 95%CI: 6.1- 71.3]. The IVE against A(H3N2) was 32.7% (95%CI: -4.3-56.5] and against B virus was 71.8% [95%CI: 50.3-84.0].

IOR varied between the factor assessed and influenza (sub)types. For chronic condition, IOR varied between 0.66 and 1.017; for age it varied between 0.47 and 1.97. However, no statistically significant effects were detected.

Table 1. Comparison between Cases, any influenza, (sub)type A(H1N1)pdm09, AH3N2 and B, and Controls, regarding seasons, age, sex, chronic conditions, smoking, hospitalizations, GP visits, help for bathing, education, cohabitants, seasonal vaccine, ILI signs and symptoms.

		Influenza				Controls
		Any	A(H1N1)pdm09	A(H3N2)	B	
Season						
2010/11, % (n/total)		54.3 (144/265)	36.3 (69/190)	1.6 (2/123)	37.6 (73/194)	45.7 (121/265)
2011/12, % (n/total)		40 (134/335)	26.8 (80/299)	39.6 (132/333)	1 (2/203)	60 (201/335)
2012/13, % (n/total)		41 (152/371)	45.5 (46/101)	2.7 (6/225)	23.2 (66/285)	59 (219/371)
2013/14, % (n/total)		56.3 (71/126)	1.9 (2/108)	31.3 (25/80)	0 (0/55)	43.7 (55/126)
2014/15, % (n/total)		58.1 (147/253)	37.2 (111/298)	29.8 (45/151)	48.5 (100/206)	41.9 (106/253)
2015/16, % (n/total)		39.9 (124/311)	0 (0/167)	1.1 (2/189)	5.6 (11/198)	60.1 (187/311)
2016/17, % (n/total)		51.6 (178/345)	16.5 (28/170)	51.6 (178/345)	0 (0/167)	48.4 (167/345)
2017/18, % (n/total)		48.7 (135/277)	100 (336/1534)	9 (14/156)	39.6 (93/235)	51.3 (142/277)
$p_a$		<0.001	<0.001	<0.001	<0.001	
Age						
0-64 years, % (n/total)		87.8 (953/1085)	92.3 (310/336)	81.9 (331/404)	90.4 (312/345)	78.5 (940/1198)
≥65 years, % (n/total)		12.2 (132/1085)	7.7 (26/336)	18.1 (73/404)	9.6 (33/345)	21.5 (258/1198)
$p^b$		<0.001	<0.001	0.155	<0.001	
Sex, male %		41.7 (452/1085)	44.4 (149/336)	42.6 (172/404)	38 (131/345)	38 (455/1198)
$p^b$		0.079	0.037	0.111	1.000	

	Influenza				Controls
	Any	A(H1N1)pdm09	A(H3N2)	B	
Chronic diseases (any), %	28.6 (310/1085)	25.0 (84/336)	32.9 (133/404)	27 (93/345)	40.3 (483/1198)
<i>p<sup>b</sup></i>	<0.001	<0.001	0.009	<0.001	
Smokers, % (n/total)	15.1 (156/1034)	21.6 (71/329)	12.2 (47/384)	11.8 (38/321)	16 (185/1154)
<i>p<sup>b</sup></i>	0.555	0.021	0.084	0.065	
Help for bathing, % (n/total)	1.3 (13/1025)	0.9 (3/323)	2.3 (9/387)	0.3 (1/315)	2.5 (29/1160)
<i>p<sup>b</sup></i>	0.042	0.126	1.000	0.012	
GP consultations last 12 mo, ≥3 % (n/total)	49.7 (525/1056)	49.5 (163/329)	49.9 (198/397)	49.7 (164/330)	60.2 (706/1172)
<i>p<sup>b</sup></i>	<0.001	0.001	<0.001	0.001	
Hospitalizations, % (n/total)	1.2 (13/1072)	1.2 (4/329)	1 (4/401)	1.5 (5/342)	1.6 (19/1188)
<i>p<sup>b</sup></i>	<0.001	<0.001	<0.001	<0.001	
Years of education, ≥7 years, % (n/total)	55.3 (583/1054)	60.7 (199/328)	53.1 (208/392)	52.7 (176/334)	48.3 (554/1148)
<i>p<sup>b</sup></i>	0.001	<0.001	0.102	0.171	
Co-habitants, ≥3, % (n/total)	50.5 (542/1074)	50.8 (168/331)	47.1 (188/399)	54.1 (186/344)	40.4 (480/1187)
<i>p<sup>b</sup></i>	<0.001	<0.001	<0.001	<0.001	
Seasonal vaccine, % (n/total)	11.1 (120/1083)	8.9 (30/336)	15.9 (64/403)	7.6 (26/344)	23.9 (285/1192)
	<0.001	<0.001	<0.001	<0.001	
Fever, % (n/total)	93.8 (983/1048)	95.4 (312/327)	91.5 (354/387)	94.9 (317/334)	76.4 (836/1095)
<i>p<sup>b</sup></i>	<0.001	<0.001	<0.001	<0.001	

		Influenza				Controls
		Any	A(H1N1)pdm09	A(H3N2)	B	
Malaise, % (n/total)		94.2 (1020/1083)	94.9 (319/336)	95.5 (385/403)	91.9 (316/344)	91.1 (1088/1194)
	$p^b$	<0.001	<0.001	<0.001	<0.001	
Headache, % (n/total)		82.6 (890/1078)	83.3 (279/335)	80 (320/400)	84.8 (291/343)	76.6 (908/1186)
	$p^b$	<0.001	0.009	0.167	0.001	
Myalgia, % (n/total)		92.5 (992/1073)	95.5 (318/333)	93.3 (374/401)	88.5 (300/339)	89.4 (1065/1191)
	$p^b$	0.013	<0.001	0.024	0.621	
Cough, % (n/total)		97.1 (1052/1084)	97.9 (328/335)	97 (392/404)	96.2 (332/345)	88.5 (1060/1198)
	$p^b$	<0.001	<0.001	<0.001	<0.001	
Sorethroat, % (n/total)		80.8 (872/1079)	78 (262/336)	81.1 (327/403)	83.2 (283/340)	86.9 (1038/1195)
	$p^b$	<0.001	<0.001	0.007	0.092	
Shortness of breath, % (n/total)		19 (205/1079)	17.8 (59/331)	19.6 (79/403)	19.4 (67/345)	21.3 (254/1191)
	$p^b$	0.174	0.167	0.479	0.499	

a) Chi-square test; b) Fisher exact test

Table 2. Influenza vaccine effectiveness (IVE) crude and adjusted, for all influenza and specific (sub)types; full data analysis and in specific chronic condition or age strata

Outcome	n	Cases (n)		Controls (n)			OR		IVE
		All	Vac	All	Vac		95%CI		(%)
All influenza									
Crude	2073	1063	120	1010	239	0.369	0.29 to 0.48	63.1	52.3 to 71.5
Adjusted <sup>(a)</sup>	2020	1034	119	986	232	0.482	0.36 to 0.65	51.8	34.8 to 64.3
Chronic condition (Yes) <sup>(b)</sup>	686	298	71	388	166	0.429	0.29 to 0.63	57.1	37.2 to 70.8
Chronic condition (No) <sup>(b)</sup>	1334	736	48	598	66	0.567	0.37 to 0.88	43.3	12.2 to 63.4
Interaction term						0.756	0.44 to 1.31		
Age≥65 <sup>(c)</sup>	331	127	62	204	137	0.493	0.30 to 0.80	50.7	19.8 to 69.8
Age <65 <sup>(c)</sup>	1689	907	57	782	95	0.465	0.32 to 0.68	53.5	32.4 to 68.0
Interaction term						1.058	0.58 to 1.95		
AH1pdm09									
Crude	922	333	30	589	147	0,351	0.22 to 0.55	64,9	45.1 to 77.6
Adjusted <sup>(a)</sup>	896	326	30	570	141	0.491	0.29 to 0.84	50.9	16.1 to 71.3
Chronic condition (Yes) <sup>(b)</sup>	306	82	17	224	106	0.413	0.21 to 0.82	58.7	18.4 to 79.1
Chronic condition (No) <sup>(b)</sup>	590	244	13	346	35	0.625	0.49 to 1.11	37.5	-35.0 to 71.0
Interaction term						0.660	0.25 to 1.11		
Age≥65 <sup>(c)</sup>	141	26	12	115	83	0.286	0.11 to 0.73	71.4	27.2 to 88.8
Age <65 <sup>(c)</sup>	755	300	18	455	58	0.611	0.33 to 1.13	38.9	-13.0 to 67.0
Interaction term						0.468	0.15 to 1.42		
AH3									
Crude	960	396	64	564	146	0,533	0.36 to 0.78	46,7	22 to 63.5
Adjusted <sup>(a)</sup>	941	389	64	552	143	0,673	0.43 to 1.04	32,7	-4.3 to 56.5
Chronic condition (Yes) <sup>(b)</sup>	353	127	35	226	100	0.614	0.35 to 1.09	38.6	-9.1 to 65.4
Chronic condition (No) <sup>(b)</sup>	588	262	29	326	43	0.747	0.41 to 1.37	25.3	-36.9 to 59.2
Interaction term						0.822	0.52 to 1.12		
Age≥65 <sup>(c)</sup>	192	71	36	121	83	0.645	0.32 to 1.29	35.5	-28.5 to 67.7
Age <65 <sup>(c)</sup>	749	318	28	431	60	0.648	0.37 to 1.13	35.2	-13.0 to 62.9
Interaction term						0.995	0.41 to 2.41		
B									
Crude	870	334	26	536	131	0,243	0.15 to 0.39	75,7	61.1 to 84.9
Adjusted <sup>(a)</sup>	832	319	25	513	125	0,282	0.16 to 0.5	71,8	50.3 to 84
Chronic condition (Yes) <sup>(b)</sup>	278	89	19	189	93	0.301	0.15 to 0.58	69.9	41.6 to 84.5
Chronic condition (No) <sup>(b)</sup>	554	230	6	324	32	0.245	0.09 to 0.66	75.5	34.5 to 90.8
Interaction term						1.017	0.67 to 1.55		
Age≥65 <sup>(c)</sup>	135	30	14	105	73	0.436	0.18 to 1.05	56.4	-5.2 to 81.9
Age <65 <sup>(c)</sup>	697	289	11	408	52	0.222	0.11 to 0.45	77.8	54.7 to 89.1
Interaction term						1.966	0.64 to 6.02		

All- all cases/ controls; Vac- vaccinated

a- Adjusted for age (cubic splines), at least one chronic condition, nr GP visits (<2; ≥2 or more) and sex

b- Adjusted for age (cubic splines), nr GP visits (<2; ≥2 or more) and sex

c- Adjusted for at least one chronic condition, nr GP visits (<2; ≥2 or more) and sex

Power calculations (supplementary material) (31) indicate that the available data would have satisfactory power (>80%) to detect an interaction term between vaccine and age in the OR scale (IOR) less than 0.4 or higher than 2.4 (i.e. IV odds ratio in the  $\geq 65$  of less than 0.4/more than 2.4-fold the IV odds ratio in the  $< 65$ ).

When looking at (sub)type virus specific models and age or chronic conditions power of at least 80% would require an IOR even lower (if  $\text{IOR} < 1$ )/higher (if  $\text{IOR} > 1$ ).

## Discussion

In this study we assessed the age and chronic conditions as potential effect modifiers of influenza vaccine effectiveness. Adjusted IVE against influenza, all and specific (sub)types, were comparable to other studies (4). When comparing to meta-analysis on influenza vaccine effectiveness by (sub)type (32), we observe a similar pattern of lower IVE estimates against A(H3) (meta-analysis results 33%; 95% CI 26-39) and higher against A(H1)pdm09 (meta-analysis results 61%; 95% CI 57-65) and against B (meta-analysis results 54%; 95% CI 46-61). These estimates are reassuring of the external consistency of our results.

While we did not find evidence of effect modification, for either studied factors, the differences in the point estimates; the width of confidence intervals and power calculations suggest that there was lack of power to detect effect modification of non-negligible magnitude. Nevertheless, the different strata point estimates provide further insights on the studied hypothesis of different IVE estimates in the chronic condition strata (when compared to no chronic condition strata) and in the older age groups (when compared to younger age groups).

For chronic conditions most results are against the hypothesis, with IVE estimates higher in the chronic condition strata. This can be due to residual confounding and/or chronic condition misclassification. For the former, we hypothesize that those with chronic condition and vaccinated are more likely to adopt additional preventive behaviors which protect them of acquiring the virus. While this would confound a possible causal interaction the differential effect of the vaccine ("effect heterogeneity") between those with/without a chronic condition would still exist and might have implications in itself (31). Regarding chronic condition misclassification we used the medical condition status to classify an individual as having a chronic condition. As such, we could not assess whether the condition was controlled or to what degree. Further research with more detailed information, on the medical condition status and medications is needed to assess these potential biases.

Regarding age, we observed higher IVE against (A(H1N1)pdm09, equal IVE against A(H3N2) and lower IVE against B virus in  $\geq 65$  comparing with  $< 65$  aged. These results are more in agreement

with what was expected. Previous exposure in life to A(H1)pdm09 was pointed as protective for the older adult population during the pandemic (33). Also, there is some evidence of reduced IVE against A(H1N1)pdm09 in the age cohort of adults born between 1958 and 1979 (34) and this may influence IVE in each age strata. Furthermore, the lower IVE against B virus estimated for the older adult population, was in accordance to the hypothesis of higher capacity of vaccine-induced immune response in younger population when compared to elderly. The results obtained against A(H3N2) virus reinforce the low capacity of trivalent inactivated vaccine to provide adequate protection against this virus (sub)type, for both younger and older adults.

There are other methodological limitations to be acknowledged. First, the power calculation were performed under the assumption of a rare outcome (30) and the frequency of vaccination does not meet this assumption. Furthermore, should have this led to an overestimation of the IOR, power might even be lower. Secondly, we have assessed multiplicative interaction and cannot exclude the hypothesis of additive interaction (31). Given the limited power this might also be explored in further studies.

## Conclusion

Our hypothesis of lower influenza vaccine effectiveness in the high-risk population was not supported neither excluded by our study. Available data sample could only identify very high effect modifications. Given the subject matter for the discussion on who to target in influenza vaccination strategies, further studies should be conducted with larger sample sizes, ensuring adequate power, and collecting other relevant data to adjust for relevant confounders.

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### Supplementary material - Interaction term and power

Assuming rare outcome assumption and taking in consideration the sample size for each outcome / interaction variable, we developed the following graphs (Figure S2 e S3). They represent the power for each interaction term (IOR), and were developed according to VanderWeele and Knol work (1).

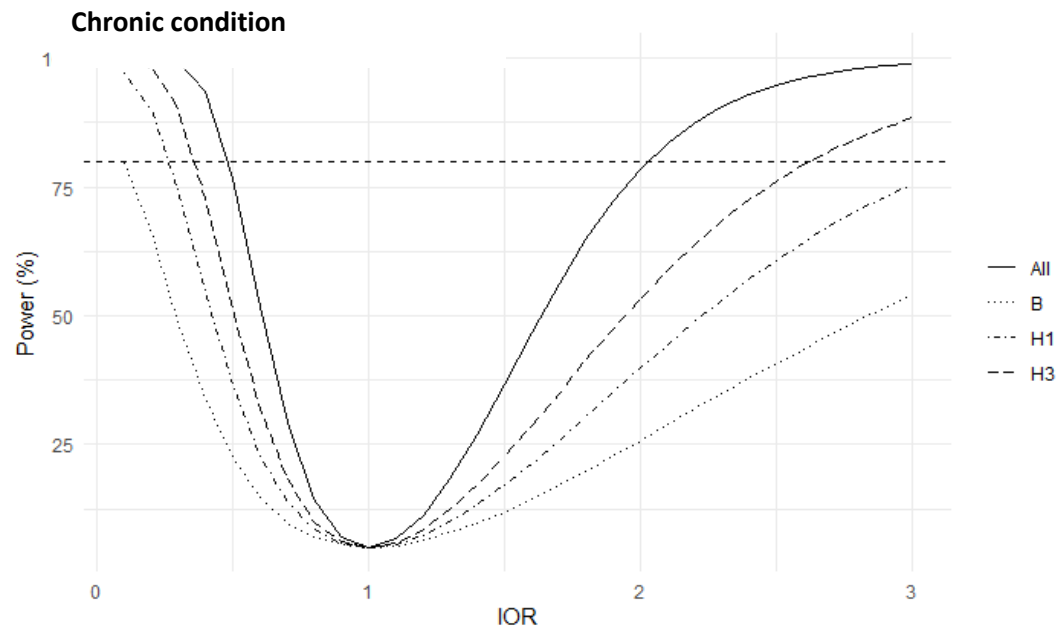


Figure S2- Power calculation for each interaction term (odd-ratio scale) (IOR) considering chronic condition as modifier factor

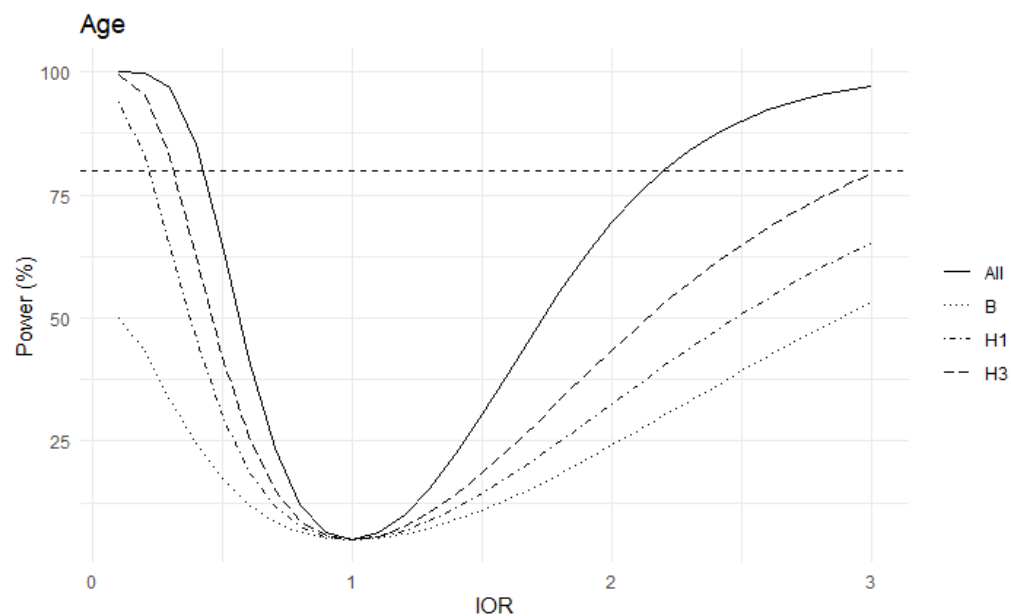


Figure S3- Power calculation for each interaction term (odd-ratio scale) (IOR) considering age as modifier factor

## **Implementing an influenza vaccine effectiveness study in a hospital context: the EVA Hospital project**

**Short title:** Implementing EVA Hospital study

**Título:** Implementação de um estudo de efetividade da vacina contra gripe no contexto hospitalar : projeto EVA hospital

**Authors:** Ausenda Machado<sup>1,2</sup>, Verónica Gomez<sup>1</sup>, António Panarra<sup>3</sup>, Jose Poças<sup>4</sup>, Rita Corte-Real<sup>3</sup>, Maria João Peres<sup>4</sup>, Baltazar Nunes<sup>1,2</sup> on behalf of EVA Hospital Group

1. Departamento de Epidemiologia, Instituto Nacional de Saúde Doutor Ricardo Jorge, I.P. (INSA)
2. Centro de investigação Saúde Pública, Escola Nacional de Saúde Pública, Universidade NOVA de Lisboa, Lisboa, Portugal
3. Centro Hospitalar Universitário Lisboa Central, E.P.E.
4. Centro Hospitalar de Setúbal, E.P.E.

*EVA Hospital Group:*

*Instituto Nacional de Saúde Doutor Ricardo Jorge*

Departamento de Epidemiologia: Irina Kislaya, Ana Paula Rodrigues

Departamento de Doenças Infecciosas: Raquel Guiomar, Pedro Pechirra, Paula Cristovão, Patrícia Conde

*Centro Hospitalar e Universitário de Lisboa Central*

Liliana Dias, Paula Branquinho, Cláudia Mihon, Ana Rita Estriga, Ana Brito, Luís Vale, Helena Pacheco, André Almeida, Helena Amorim

*Centro Hospitalar de Setúbal*

Paula Lopes, Vitor Augusto, Rosa Ribeiro, Regina Viseu

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**Corresponding author** Ausenda Machado, [ausenda.machado@insa.min-saude.pt](mailto:ausenda.machado@insa.min-saude.pt), **Full postal address:** Instituto Nacional de Saúde Doutor Ricardo Jorge, Av. Padre Cruz, 1649-016, Lisbon, Portugal

## Abstract

### Background

The project 'Integrated Monitoring of Vaccines in Europe' aimed to measure seasonal influenza vaccine effectiveness against hospitalised adults,  $\geq 65$  years, with influenza. We describe the protocol implementation in Portugal.

### Methods

We implemented a test-negative design, targeting community-dwelling patients aged  $\geq 65$  years hospitalised with Severe Acute Respiratory Illness (SARI). Patients were RT-PCR tested for any influenza. Cases were those positive for influenza; negative were controls. Most variables were collected using hospital medical records. Selection bias was evaluated by comparison with the laboratory influenza requests database according to demographic characteristics. Crude, season-adjusted influenza vaccine effectiveness (IVE) was estimated as  $IVE = 1 - OR$  (odds ratio), and 95% confidence intervals (CI) were obtained by conditional logistical regression, matched with the disease onset month.

### Results

The recruitment rate was 37.8%. The majority of participants ( $n = 368$ ) were female (55.8%) and aged  $\geq 80$  years (55.8%). This was similar to values for potentially eligible SARI patients ( $\geq 80$  years: 56.8%, female: 56.2%). The proportion of missing values was below 2.5% for 20 variables and above 5% (max. 11.6%) for six variables. IVE estimates were 62.1% against AH1pdm09 (95% CI: -28.1 to 88.8), 14.9% against A(H3N2) (95% CI: -69.6 to 57.3), 43.6% against B/Yam (95% CI: -66.2 to 80.8).

### Conclusions

Despite the low participation rate, we observed comparable characteristics of participants and eligible SARI patients. Data quality was high, and IVE results were in accordance with meta-analysis results and European pool season-specific estimates. The final sample size was low, which inhibited obtaining estimates with good precision.

### Resumo

O projeto "Integrated Monitoring of Vaccines in Europe" pretende medir a efetividade da vacina antigripal nas hospitalizações por gripe nos com  $\geq 65$  anos. Este estudo pretende descrever a implementação do protocolo em Portugal.

Implementou-se um estudo com desenho caso-controlo teste negativo. A população-alvo foram indivíduos com  $\geq 65$  anos, hospitalizados com doença respiratória aguda grave. Os doentes foram testados para gripe por RT-PCR. Foram considerados casos aqueles com resultado positivo; os restantes foram controlos. Os dados foram obtidos através de registo clínicos. O potencial viés de seleção foi avaliado por comparação de características demográficas e enfermarias com dados das requisições laboratoriais. A efetividade da vacina,

foi estimada 1–*Odd-Ratio* por regressão logística condicional, emparelhada para o mês de início da doença.

A taxa de recrutamento foi de 37,8%. A maioria dos participantes (n=368) era do sexo feminino (55,8%) e tinha ≥80 anos (55,8%). Padrão similar foi verificado nos doentes elegíveis (≥80 anos: 56,8%; feminino: 56,2%). Os valores omissos foram inferiores a 2,5% em 20 variáveis e acima de 5% (máx. 11,6%) em 6 variáveis. As estimativas da efetividade foram 62,1% contra AH1pdm09 (Intervalo de Confiança IC95%: -28,1, 88,8); 14,9% contra A (H3) (IC 95%: -69,6; 57,3) e 43,6% contra B/yamagata (IC 95%: -66,2; 80,8).

Apesar da baixa taxa de participação, observamos características comparáveis entre os participantes e os doentes elegíveis. A qualidade dos dados foi elevada, e os resultados da efetividade concordantes com resultados de meta-análise e estimativas do Europeias. A reduzida dimensão da amostra impediu obter estimativas mais precisas.

Keywords: SARI, influenza vaccine effectiveness, selection bias, internal and external validity

## Introduction

For the decade before 2020, estimating the influenza vaccine effectiveness (IVE) has been of extreme importance to evaluate the benefits of the influenza vaccine in reducing the disease. In Portugal, observational studies in the primary care setting have been implemented using the test-negative design and using a cohort in the community setting <sup>1,2</sup>. The older adults, aged 65 years and older, are an important target of these studies, considering the expected effectiveness of the vaccine in not only reducing the infection but also reducing most related hospitalisations and even death <sup>3,4</sup>.

Using the primary care setting, it was possible to have an overview of the vaccine protection level against medically attended laboratory-confirmed influenza. When comparing IVE estimates to prevent medically attended influenza between an older adult population and younger adults, point estimates tended to be lower for the oldest group, despite being not significant <sup>5,6</sup>. The extended protection provided by the influenza vaccine against severe cases that require hospitalisation was expected to be greater. Severe cases that require hospitalisation constitutes an average of 64% of influenza-related pneumonia and influenza hospitalisations each year <sup>7</sup>.

To evaluate IVE against this severe outcome required changing the research setting. Since 2011, a European hospital network has been implementing, yearly, a common protocol using the test-negative design <sup>8,9</sup>. A variety of hospitals and recruitment processes were included. According to the authors of the pilot study, the most successful hospitals in collecting data had either a surveillance system in place or systematic selection algorithms with dedicated staff specifically for the study <sup>8</sup>. Other IVE studies have also been implemented with the common ground of the existence of hospital-based surveillance systems <sup>10</sup>.

In Portugal, influenza vaccination has been available free of charge to the population aged 65 years and older since 2012. Approximately 75% of the vaccinated older adults received their vaccinations in primary care centres <sup>11</sup>. Vaccines that are administered at the health centre are registered in *Sinus/e-Vacinas* and made available on the *Health Data Platform*, which can be accessed by health professionals using their individual's National Health Service user number. Thus, there was potential for designing and implementing a hospital-based IVE study in Portugal that could be set up on a yearly and seasonal basis, providing timely and accurate data for the pooled seasonal influenza vaccine protection estimates.

Within the IMOVE+ (Integrated Monitoring of Vaccines in Europe) project, a study was designed and implemented in Portugal (EVA Hospital study). This research paper aims to describe the implementation in Portugal of the IVE study targeting the 65 years and older population during three consecutive seasons (2015/16 to 2017/18) and evaluation of its internal and external validity in two Portuguese hospitals.

## **Methods**

### *Study design*

We used a hospital-based test-negative design (TND), in which influenza vaccine coverage in patients with a severe acute respiratory infection (SARI) with laboratory-confirmed influenza was compared to influenza vaccine coverage in laboratory-confirmed influenza-negative SARI patients.

### *Setting*

The study was implemented during three consecutive seasons, from 2015/16 (pilot season) to 2017/18, in two hospitals in the Lisbon area. SARI patients were recruited in Centro Hospitalar e Universitário de Lisboa Central (CHULC, a tertiary referral hospital) and Centro Hospitalar de Setúbal (CHS, a medium-capacity hospital). Detailed information on the participating hospitals and respective wards is provided in the Supplementary material (Table S1).



### *Study population*

The study population consisted of all community-dwelling individuals aged 65 years and older, hospitalised with SARI in one of the participating hospitals and wards, without contraindication for influenza vaccination.

Following the TND IVE hospital protocol <sup>9</sup>, patients were eligible for participation according to SARI definition: hospitalised (>24 hours) and presenting at least one systemic symptom (fever, myalgia, malaise, headache, or general deterioration) and one respiratory symptom (cough, sore throat, or shortness of breath).

In both hospitals, SARI patients were first identified following a laboratory request for influenza detection and were included in the study after providing written informed consent. Exclusion criteria included institutionalisation, SARI symptoms onset more than 48 hours after admission (i.e., nosocomial SARI), positive testing for influenza before recruitment within the season (i.e., previous influenza) and antiviral treatment between symptoms onset and swab testing. Exclusions of potential participants meeting exclusion criteria were recorded in seasons 2016/17 and 2017/18.

### *Definition of cases and negative controls*

A SARI patient was considered as a 'case' if a respiratory sample collected within 7 days of symptom onset and admission was positive for an influenza virus (A or B). 'Negative controls' were SARI patients with a respiratory sample that tested negative for any influenza virus. Influenza diagnosis was conducted at the hospital laboratories using RT-PCR.

### *Data collection*

All relevant epidemiological data were collected using a standardised questionnaire completed by the physician at the hospital ward. The data sources included hospital medical records, *Health Data Platform (Plataforma de Dados de Saúde – PDS)*, and hospital laboratory records. Interviews with patients relatives were used as a last resource. The questionnaire included patient demographics, SARI signs and symptoms and date of disease onset, dates of admission, swabbing and discharge, a list of underlying chronic conditions, number of hospitalisations for chronic diseases in the previous 12 months and number of GP visits in the previous 3 months, smoking status, antiviral administration, pneumococcal vaccination status and laboratory results. All data collection was performed by a medical doctor, and no dedicated full-time staff was used to perform these procedures.

The main exposure variable of interest was influenza vaccine uptake in the current season, and a patient was considered vaccinated if the vaccination occurred at least 14 days before SARI onset. Influenza vaccine uptake in the previous season was also collected.

#### *Data management*

Validated anonymised questionnaires were centrally collected by the Department of Epidemiology at the National Health Institute Doutor Ricardo Jorge, where all data were double-entered.

#### *Sample size*

The minimum sample size was calculated to be 516 SARI patients per season. This sample size was obtained assuming a vaccination coverage of 50% among the source population aged 65 years and older <sup>11</sup> and a proportion of positive for influenza of 30% among swabbed SARI patients. This corresponded to a minimum of 155 influenza cases and 361 controls in each of the strata, to estimate an odd-ratio (OR) of 0.4 with a power of 80% and a precision of 20%.

#### *Statistical analysis*

Descriptive statistics were computed. The participation and recruitment rate for the total of seasons 2016/17 and 2017/18 was computed considering participants and the total of eligible (with known or unknown criteria) SARI patients. Potential selection bias was evaluated considering the sampling fraction calculated as the proportion of the number of included participants to the number of individuals in each hospital's laboratory influenza requests database. The descriptive comparison of participants and all potential SARI patients was done according to International Standard Organization (ISO) week within each season, demographic characteristics using Chi-Square One-Sample Goodness-of-Fit. Overall data quality was evaluated according to the proportion of missing data.

Participant baseline characteristics of cases and negative controls were computed using the Fisher's exact test or the Mann–Whitney test, depending on the nature of the variable. Crude vaccine effectiveness was estimated as  $IVE = 1 - OR$  (odds ratio, obtained by conditional logistical regression, matched to the week of onset and season), and exact 95% confidence interval was computed around the point estimate. IVE results are reported as percentages.

#### *Ethical issues and data protection*

The study protocol was approved by the National Committee of Data Protection (30 June 2015) and approved by the Ethics Committee of INSA (22 May 2015) and by the ethics committees of both participating hospitals (CHLC: 1 October 2015 and CHS: 7 January 2016).

## Results

### Participants

A total of 1423 swabs was requested for influenza detection in the 2016–2018 period by the two hospitals. Among them, approximately one third (580) was not eligible for the study, since the hospital stay was <24 hours. The total of potentially eligible SARI patients was 843 (Figure 1). Considering that for 478 SARI patients the eligibility criteria were not confirmed, and three did not consent, the total number of eligible patients (both confirmed and unknown criteria) was 773, which corresponds to a recruitment rate of 37.8%.

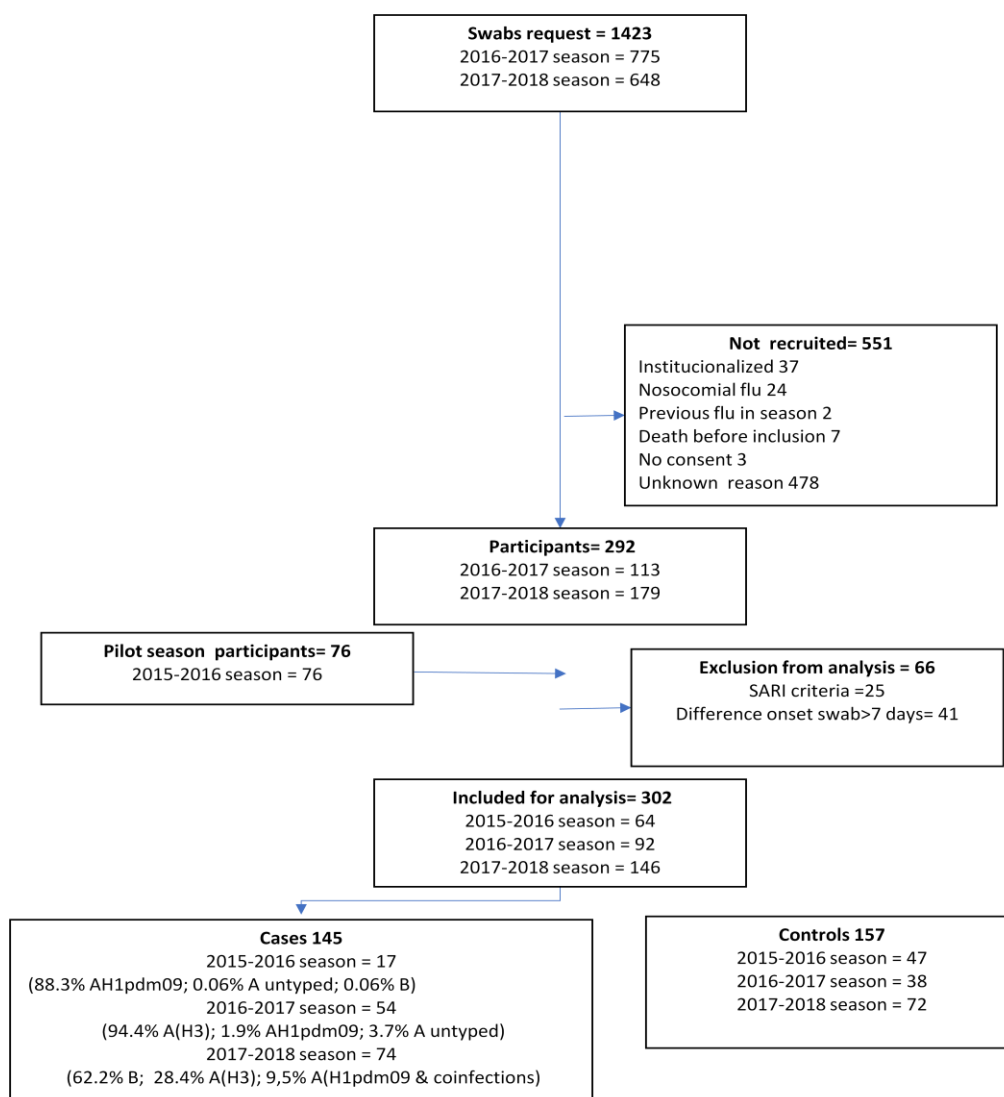


Figure 1. Flow diagram of EVA Hospital participants

The weekly distribution of the 2016/17 and 2017/18 seasons' participants (n = 292) and all potential SARI patients (n = 1423) (Supplementary material, Figure S1) reveals participants

were selected during the course of the season and followed the pattern of the seasonal epidemic.

Comparing sex and age characteristics of participants and all potential SARI patients (Table 1) indicates that both groups had a similar demographic distribution.

Table 1. Comparison of participants and all potential SARI patients according to sex, age group, and hospital ward.

	Potential SARI patients (n=1423)		Participants (n=292)		p-value*
	n	%	n	%	
<b>Sex</b>					<b>0.7918</b>
Female	800	56.2	163	55.8	
Male	623	43.8	129	44.2	
<b>Age group</b>					<b>0.5982</b>
65-79 years	615	43.2	129	44.2	
80+ years	808	56.8	163	55.8	

\*p-value of the Chi-Square One-Sample Goodness-of-Fit Tests

#### *Descriptive data*

Considering the three seasons, 368 SARI patients accepted participation in the study. From the participant pool of individuals (n = 368), 66 were excluded from the analysis, mainly due to the time delay between onset of symptoms and swab (41 out of 66).

302 SARI patients were then included in the analysis, 147 were positive for an influenza virus and were classified as 'cases', and 157 were negative controls. Season 2017/18 was the main contributor to cases and controls for the overall analysis. The weekly distributions of cases and controls (Supplementary material, Figure S1) indicate that influenza-positive SARI patients were detected between weeks 50/2015 and 8/2016, weeks 46/2016 and 4/2017 and weeks 47/2017 and 17/2018.

A comparison of cases and controls (Table 2) shows that both groups only differed for some SARI symptoms (fever, cough, general deterioration and shortness of breath) and chronic conditions (dementia and the presence of two or more chronic conditions). For all of the previous, except for fever and cough, the frequency was statistically higher in controls than in cases.

#### *Influenza vaccine*

Overall, seasonal influenza vaccine coverage was higher in controls than in cases, although not statistically significant (Table 2). Previous season vaccine uptake was higher in cases (48.4%) than in controls (46.4%) but was not significant ( $p = 0.806$ ). Other vaccines were also recorded, namely the pneumococcus vaccine (23 -valent pneumococcal polysaccharide vaccine [PPV23] and 7/10 or 13-valent pneumococcal conjugate vaccine [PCV7/10 or 13]). The PPV23 vaccine was only marginally non-significant and was more frequently reported for controls than cases.

Table 2. Comparison of cases and controls in EVA Hospital study according to the season, demographic characteristics, dependency, chronic conditions, health care use and SARI symptoms, influenza and pneumococcal vaccination status,

	Missing value (%)	Influenza	Controls	p-value
Season	0.0	145	157.0	<0.001
2015 , %		11.7	29.9	
2016 , %		37.2	24.2	
2017 , %		51	45.9	
Age, median (total)	0.0	81.0 (145)	80.0 (157)	0.643 <sup>a</sup>
65-79 years, % (n/total)		44.8 (65/145)	44.6 (70/157)	1
≥80 years, % (n/total)		55.2 (80/145)	55.4 (87/157)	
Sex, male % (n/total)	0.0	42.1 (61/145)	44 (69/157)	0.816
Smokers, % (n/total)	0.0	10.3 (15/145)	8.9 (14/157)	0.700
Dependency* , % (n/total)	0.0	52.4 (76/145)	56.7 (89/157)	0.489
2 or more chronic conditions , % (n/total)	0.7	67.4 (97/144)	78.9 (123/156)	0.027
Diabetes , % (n/total)	0.3	33.3 (48/144)	32.5 (51/157)	0.903
Chronic liver disease , % (n/total)	0.0	2.1 (3/145)	1.9 (3/157)	1.000
Heart disease , % (n/total)	1.0	58.0 (83/143)	59.0 (92/156)	0.907
Hematologic cancer, % (n/total)	0.7	3.5 (5/143)	5.1 (7/157)	0.578
Immunodeficiency and organ transplant , % (n/total)	11.6	2.3 (3/133)	5.2 (7/134)	0.334
Lung disease , % (n/total)	1.3	38.0 (54/142)	44.2 (69/156)	0.291
Nonhematologic cancer , % (n/total)	0.3	13.2 (19/144)	11.5 (18/157)	0.726
Nutritional deficiencies , % (n/total)	3.0	4.2 (6/144)	4.0 (6/150)	1.000
Renal disease , % (n/total)	1.0	16.8 (24/143)	22.4 (35/156)	0.246
Dementia, stroke , % (n/total)	1.0	13.9 (20/144)	25.2 (39/155)	0.020
Rheumatologic diseases , % (n/total)	2.6	9.8 (14/143)	12.6 (19/151)	0.467
Obesity , % (n/total)	0.7	24.3 (35/144)	32.7 (51/156)	0.126
GP consultations last 3 mo , median (total)	2.6	1.0 (138)	1.0 (156)	0.723 <sup>a</sup>
Hospitalizations , median (total)	0.0	0.0 (145)	0.0 (157)	0.596 <sup>a</sup>
Fever, % (n/total)	4.6	78.1 (107/137)	64.2 (97/151)	0.013
Malaise, % (n/total)	1.0	85.9 (122/142)	86.6 (136/157)	0.868
Headache , % (n/total)	6.3	24.1 (32/133)	25.3 (38/150)	0.89
Myalgia , % (n/total)	6.3	64.7 (88/136)	54.4 (80/147)	0.090
Cough , % (n/total)	1.0	97.2 (138/142)	89.2 (140/157)	0.007

	Missing value (%)	Influenza	Controls	p-value
Sorethroat , % (n/total)	4.6	19.1 (26/136)	16.5 (25/152)	0.643
General deterioration , % (n/total)	1.0	68.5 (98/143)	79.5 (124/156)	0.034
Shortness of breath , % (n/total)	0.7	72.9 (105/144)	89.7 (140/156)	<0.001
Influenza vaccine, % (n/total)	3.3	39.4 (56/142)	44.0 (66/150)	0.477
Influenza vaccine (previous season),% (n/total)	11.9	48.4 (61/126)	46.4 (65/140)	0.806
PPV23 vaccination, % (n/total)	10.6	2.3 (3/133)	8.0 (11/137)	0.051
PCV7/10 or 13 vaccination , % (n/total)	16.6	3.3 (4/121)	6.1 (8/131)	0.381

p-value for Fisher' exact test except for <sup>a</sup> Mann-Whitney test

\*Defined as if the Patient has difficulty doing at least one of the actions of Barthel Index

### Main results

Crude IVE point estimates indicate that the vaccine reduced by 32.1% (95% CI: -18.6 to 61.1) the risk of SARI due to influenza during the seasons in the study (Table 3). Influenza virus type-specific estimates indicate that the seasonal IVE was 79.4% against AH1pdm09 (95% CI: -4.2 to 95.9), 13.3% against A(H3) (95% CI: -80.7 to 58.4) and 52.9% against B/Yam (95% CI: -56 to 85.8). None of these estimates was significant.

Table 3. Influenza vaccine effectiveness (IVE) against influenza and type/subtype influenza in 2015-2016 to 2017-2018 seasons

	OR	95%CI	IVE* = (1-OR)	95%CI
Any Influenza	0.68	0.39 to 1.19	32.1%	-18.6 to 61.1
AH1pdm09	0.21	0.04 to 1.04	79.4%	-4.2 to 95.9
AH3	0.87	0.42 to 1.81	13.3%	-80.7 to 58.4
B/Yam	0.47	0.14 to 1.56	52.9%	-56 to 85.8

\*conditional logistic regression model, match for week of onset and season

OR- Odd-Ratio

IVE- Influenza vaccine effectiveness

95%CI- 95% confidence interval

### Discussion

In this study, we evaluated several features of the EVA Hospital implementation. The identification, eligibility, and recruitment of SARI patients were the first item. The rationale for this evaluation was to explore potential selection bias that could result in biased IVE estimates and also impair results generalisability <sup>12</sup>. According to our results, participants were comparable to overall potential patients that required hospitalisations with respiratory illness. For these patients, a nasopharyngeal swab was taken, as the clinical guidelines indicate that in the influenza season ambulatory patients over 65 years of age and patients admitted with severe respiratory symptoms and/or acute fever must be tested in order to obtain laboratory confirmation for influenza <sup>13</sup>.

This comparable pattern was observed in both the sociodemographic characteristics of the patients and the time within the season. This last feature is of particular importance, considering that the outcome of interest is time-dependent (influenza epidemic) and the positivity ratio varies considerably during the course of the season. Taking into consideration that we used the test-negative design, all the previous assumptions can affect the IVE estimate. The test-negative design has been widely used in IVE monitoring studies, since it is easy to implement and minimises confounding by health-seeking behaviour <sup>14,15</sup>. These features combined with a specific outcome such as laboratory-confirmed influenza, reassure the assessment of unbiased IVE estimates <sup>12</sup>. However, the use of such a type of design does not impair the evaluation of other types of bias, either selection, information or confounding, that could arise from the implementation process. Particularly, this is true when ultimately there is the objective of pooling the data across different sites <sup>12</sup> to obtain broader and more precise IVE estimates. Assessing the study implementation (for its internal and external validity) is needed to make the study results, their interpretation and their use for public health action robust. The results obtained in our study partially assure minimised selection bias in the context of the SARI identification approach used in the EVA Hospital project. It should be noticed that this is only plausible considering the SARI identification approach that was used in the study, i.e., the requirement of a swab request. The European common protocol <sup>16</sup> anticipates the identification of patients using admission registries and provides International Classification of Diseases (ICD) 9 and 10 version SARI codes. In the EVA Hospital study, the selected approach was the feasible one, given the non-existence of a codified admission database in either participating hospital.

Considering external validity, the results obtained are only valid for the older adult population residing in the two participating hospitals' catchment area who recur to a public hospital with severe influenza or SARI symptoms. There are several private hospitals in the Lisbon area that

could be accessed by the same population, and this could be a limitation of our setting. Nevertheless, it should be taken into consideration that older adults have a lower probability of having private health insurance and thus lower probability of hospital admissions in private hospitals.

Overall eligibility criteria were assessed for approximately two-thirds of the individuals with a swab request in seasons 2016–2017 and 2017–2018. In the 2015–2016 season, such a mechanism was not available, since it was a pilot study. This eligibility evaluation was mainly done retrospectively, at the end of each season, a fact that may explain the non-negligible number of individuals with unknown eligibility criteria (473 out of 843). Considering that the recruitment (participation) rate is the proportion of participants out of the total of individuals eligible for the study (all swabbed individuals according to each hospital laboratory database), the overall participation rate was calculated to be approximately 38%. This value is comparable to the ones obtained in the European hospital network pilot study, which ranged between 6.9 and 52.7% participants out of those screened <sup>8</sup>.

After exclusion, the final sample of participants for analysis was 302, all three seasons considered. Given that the minimum sample size per season was calculated as 516 SARI patients, this constitutes a major constraint of the study.

We found no significant differences between cases and controls for the majority of analysed variables. The rationale for these results pertain to the severity of the outcome (hospitalisation) that makes characteristics more homogenised; thus, it may be due to common risk factors and may not be influenza-specific.

The overall quality of data indicates that missing data was residual in the main variables of the database. As for the main exposure of interest, influenza vaccination status was collected using the PDS. The access to this platform was extremely valuable for collecting and validating patients' information. This platform was easily accessed by the health professional and included vaccination data (present and past season influenza and pneumococcal vaccine). All the influenza vaccinations that were done in the health centre were registered in this database. For the population aged 65 and older who lived in the Lisbon hospitals area, the proportion vaccinated in the health centre was 68% in the 2015/16 season and 67% in the 2017/18 season <sup>17,18</sup>. Given this above-average proportion of older adults who prefer this location for the vaccine uptake, there was a high probability of getting the correct information (date and brand included). Assuming a non-differential misclassification of the vaccine uptake, the impact on IVE estimates was determined to be negligible (Supplementary material).



However, for the pneumococcal vaccine, the situation was different. The vaccine coverage is low in Portugal, and the PPV or PCV vaccination could precede the PDS creation.

The use of electronic registries is, on one hand, extremely facilitating in compiling an individual health record. On the other hand, given that their information is not structured and relies on reporting by a health professional, there could be differential quality of information. In the primary care units, in the five years leading to 2020, there has been a huge increment of data that has been registered, and its quality and completeness are important for achieving the contracted targets. This being the case, registries at this care level are incrementing. Data at hospital level was collected prospectively, and relevant data was collected by the participating medical doctors, who were trained for data collection.

Concerning laboratory results, they were obtained using high-sensitivity and high-specificity RT-PCR<sup>19</sup>, and both hospital laboratories are part of the Portuguese Laboratory Network for Influenza Diagnosis and participate in the National External Quality Assessment Programme for influenza detection, with high scoring evaluations. Consequently, misclassification of main exposure and outcome is expected to be residual, if any..

Conditional logistic regression IVE point estimates were in line with the results from meta-analysis studies in which summary IVE was determined as 54% for A(H1N1)pdm09, 33% for A(H3N2) and 31% for B influenza<sup>20</sup>. Due to the small sample size, our estimates had severe imprecision problems.

The EVA Hospital study was implemented in seasons 2015/16 to 2017/18, with evaluation results indicating that selected participants were comparable to potential SARI patients. Moreover, misclassification of main exposure and outcome was probably residual, if any. The IVE point estimates were in accordance with meta-analysis results and European pool season-specific estimates. The Portuguese contribution to the European IVE hospital network had consistent internal validity. The main issue that needs to be improved, and that will enable obtaining higher-precision estimates, is the sample size. It is important that recruitment rate increases the number of potential participants for which eligibility is unknown. Adding dedicated fieldwork staff may be a way to improve this process indicator. Another way to increase sample size is to include other hospitals and wards, and thus increase the size of the Portuguese hospital network and thereby increase national representativeness.

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## Supplementary material

**TABLE S1. DESCRIPTION OF PARTICIPATING HOSPITALS, WARDS AND PERIOD OF RECRUITMENT, BY SEASON.**

	Period of SARI participants recruitment			Wards included
	2015-2016	2016-2017	2017-2018	
CHULC	Week 50/2015 to week 17/2016	Week 46/2016 to week 17/2017	Week 47/2017 and ended into 17/2018	Internal medicine (subdivided into 10 wards)
CHS	Week 1/2016 to week 17/2016			Emergency, Infectiology, Pneumology, Internal medicine, and ICU

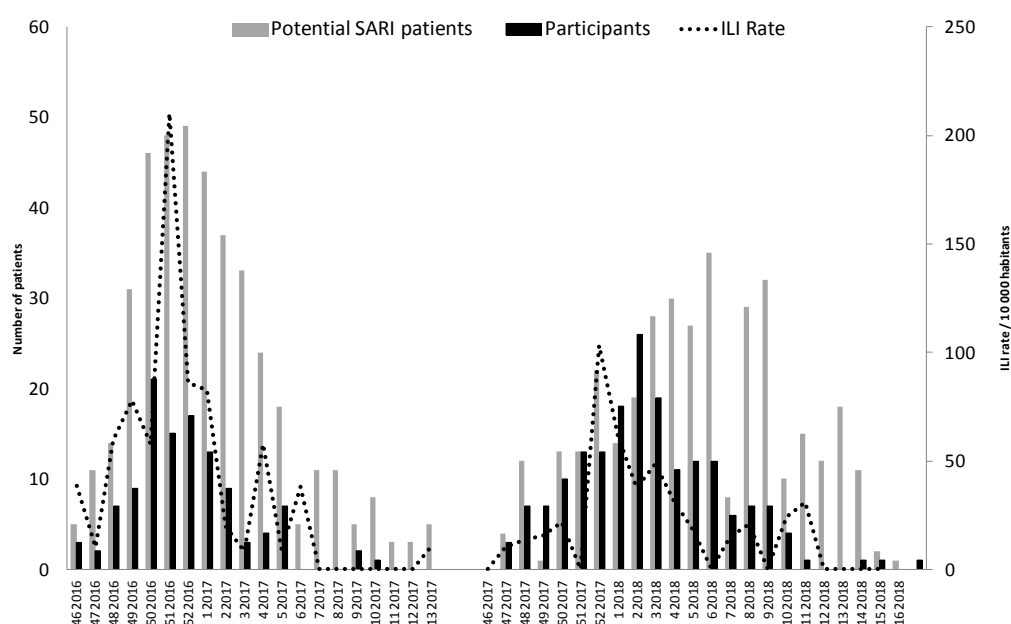


Figure S1. Weekly distribution of participants and potential SARI patients according to swab date; influenza like-illness (ILI) rate from primary care influenza surveillance system

Table S2. Sensitivity analysis for IV uptake misclassification (crude OR and IVE)

	VC cases	VC controls	OR	IVE
EVA Hospital	0.4	0.44	0.85	0.15
Correcting for proportion of vaccinated at the Health center (67%)	0.60	0.66	0.77	0.23

### 5.3 Impact of influenza vaccination strategy

"What is the population impact of the IV strategy? " was the last research questions and two studies were developed to answer to it.

Study 5, "*Impact of influenza vaccination programmes among the elderly population on primary care, Portugal, Spain and the Netherlands: 2015/16 to 2017/18 influenza seasons*", is focused on adults with 65 and more years. It resulted from a collaboration of three European countries committed on an effort to develop and implement an harmonized protocol to measure the impact of influenza vaccination program on medically-attended.

Study 6, "*Impact of national influenza vaccination strategy in severe influenza outcomes among the high-risk Portuguese population*", addresses the high-risk population (adults with 65 and more years and < 65 years with a chronic condition) and provides the results on the impact of the influenza vaccination program on severe influenza outcomes.



## Impact of influenza vaccination programmes among the elderly population on primary care, Portugal, Spain and the Netherlands: 2015/16 to 2017/18 influenza seasons

Ausenda Machado<sup>1,2,3</sup>, Clara Mazagatos<sup>2,4</sup>, Frederika Dijkstra<sup>2,5</sup>, Irina Kislaya<sup>1,3</sup>, Alin Gherasim<sup>4</sup>, Scott A McDonald<sup>5</sup>, Esther Kissling<sup>6</sup>, Marta Valenciano<sup>6</sup>, Adam Meijer<sup>5</sup>, Mariëtte Hooiveld<sup>7</sup>, Baltazar Nunes<sup>1,3</sup>, Amparo Larrauri<sup>4</sup>

1. National Institute for Health Doutor Ricardo Jorge, Epidemiology department, Lisbon, Portugal
2. These authors contributed equally
3. NOVA National School of Public Health, Public Health Research Centre, Universidade NOVA de Lisboa, Lisbon, Portugal
4. National Centre of Epidemiology, Carlos III Health Institute, CIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain
5. National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
6. Epidemiology department, Epiconcept, Paris, France
7. Nivel, Netherlands Institute for Health Services Research, Utrecht, the Netherlands

**Keywords:** *influenza*; influenza vaccine; impact; averted cases

### Abstract

**Background:** To increase the acceptability of influenza vaccine, it is important to quantify the overall benefits of the vaccination programme.

**Aim:** To assess the impact of influenza vaccination in Portugal, Spain and the Netherlands, we estimated the number of medically attended influenza-confirmed cases (MAICC) in primary care averted in the seasons 2015/16 to 2017/18 among those  $\geq 65$  years.

**Methods:** We used an ecological approach to estimate vaccination impact. We compared the number of observed MAICC (n) to the estimated number that would have occurred without the vaccination programme (N). To estimate N, we used: (i) MAICC estimated from influenza surveillance systems, (ii) vaccine coverage, (iii) pooled (sub)type-specific influenza vaccine effectiveness estimates for seasons 2015/16 to 2017/18, weighted by the proportion of virus circulation in each season and country. We estimated the number of MAICC averted (NAE) and the prevented fraction (PF) by the vaccination programme.

**Results:** The annual average of NAE in the population  $\geq 65$  years was 33, 58 and 204 MAICC per 100,000 in Portugal, Spain and the Netherlands, respectively. On average, influenza vaccination prevented 10.7%, 10.9% and 14.2% of potential influenza MAICC each season in these countries. The lowest PF was in 2016/17 (4.9–6.1%) with an NAE ranging from 24 to 69 per 100,000.

**Conclusions:** Our results suggest that influenza vaccination programmes reduced a substantial number of MAICC. Together with studies on hospitalisations and deaths averted by influenza vaccination programmes, this will contribute to the evaluation of the impact of vaccination strategies and strengthen public health communication.

### Background

Influenza infections cause considerable morbidity and mortality [1,2], in particular among the elderly population 65 years and older. Vaccination is considered the most important public health intervention to reduce the incidence of seasonal influenza and its associated complications [3]. Following the World Health Organization recommendations [4], most

European countries have a yearly influenza vaccination programme targeting, among others, individuals aged 65 years and older [5]. In most European Union (EU) countries, vaccine coverage (VC) in individuals in high-risk groups is below the target of 75% set by the EU Council [6].

To increase the acceptability of the influenza vaccine, it is important to assess the benefits of vaccination. Since 2008, influenza vaccine effectiveness (IVE) studies conducted every season in the EU suggest that the effectiveness of the vaccine is low to moderate in the elderly population [7,8]. These estimates provide useful information for scientists, but could be less comprehensible for the general public and for policymakers.

Estimating the impact of the influenza vaccination campaign focusing on the overall effect of the vaccine in the population has been an approach used by several countries [2,9-12]. Preaud et al. took a multi-country approach at European level [13]. In that study, the authors evaluated the public health and economic benefits of influenza vaccination, quantifying the prevented cases of influenza, hospitalisations and deaths in target groups for vaccination. They used country-specific data, when available, and interpolated data otherwise, that covered different seasons according to the different parameters. These authors quantified the differences in the number of influenza-confirmed associated events between the population exposed and the population not exposed to the vaccination programme using three parameters: IVE, VC and number of observed events. Impact was expressed as the number of influenza associated events averted by the influenza vaccination programme. These impact indicators to evaluate vaccine performance are easy to understand and to interpret.

To compare the number of averted events (NAE) in different countries with similar but not equivalent vaccination strategies, it is important to have not only a common approach but also harmonised parameter criteria. The lack of country-specific data limited the comparison of the impact of European influenza vaccination programmes [13]. Therefore, we developed a common protocol within the I-MOVE+ project [14] with a harmonised methodology that could measure, in different countries, the impact of the influenza vaccination programme. In this study, we aimed to assess the impact of the influenza vaccination programmes in Portugal, Spain and the Netherlands, by measuring the number of medically attended influenza-confirmed cases (MAICC) in primary care averted by vaccination, among the population aged 65 years and older, in three consecutive seasons (2015/16 to 2017/18). This was done by integrating existing estimates into new measures that may be more meaningful for public health policymakers and the public.

## Methods

### *Study design*

We developed an ecological study to estimate the number of medically attended influenza averted by the influenza vaccination programme.

We computed the number of averted events as:

$$NAE = n \times \frac{VC \times IVE}{1 - (VC \times IVE)}$$

where n is the number of observed MAICC. To enable comparison between countries, NAE was also presented per 100,000 population. We estimated the prevented fraction as



$PF = NAE/(n + NAE)$ . In addition, we calculated number needed to vaccinate (NNV) to prevent one MAICC, using methodology described in the Supplementary material.

### **Input data**

#### **Influenza vaccination strategy**

In the seasons 2015/16 to 2017/18, trivalent inactivated influenza vaccines were available for the population 65 years and older in the three countries. All countries had a national seasonal influenza vaccination programme in place and influenza vaccination was recommended for high-risk individuals (older age groups and individuals with chronic medical conditions) (Table 1). Seasonal influenza vaccination was recommended free of charge to individuals older than 60 years in the Netherlands, older than 60 or 65 years (depending on the region) in Spain, and 65 years and older in Portugal.

#### **Medically attended influenza-confirmed cases at primary care level**

To estimate the number of observed MAICC, we combined epidemiological and virological data routinely collected by country-specific sentinel influenza surveillance systems (Table 1) during the surveillance epidemic period (week 40 to week 20). For Portugal, end-of-season cumulative ILI incidence rates in the seasons 2015/16 to 2017/18 were adjusted by end-of-season influenza positivity rate in the respective season and extrapolated to the national population aged 65 years and older. For Spain, weekly ILI and positivity rate were used to obtain ILI and number of positive cases. For the Netherlands, the observed number of MAICC was estimated using a component of an evidence synthesis modelling framework that integrates data on ILI incidence, influenza positivity rate and sensitivity of virological testing and is routinely used for estimating seasonal influenza incidence in the Netherlands [15]. Virus shedding peaks around 1 to 2 days after onset of symptoms, after which – for healthy persons – it usually declines to undetectable levels 7 days after onset of symptoms [15]. Therefore, we restricted the laboratory diagnostic data from the Netherlands to those patients diagnosed with ILI from whom a specimen had been collected not more than 7 days after symptom onset. For Spain and Portugal this restriction is not applied in the surveillance system. In both countries, the great majority of ILI patients recruited by sentinel general practitioners (GPs) were swabbed within the first 7 days after onset of symptoms (> 93%). ILI data were obtained from national sentinel GP networks (the Dutch Nivel Primary Care Database, the Spanish Influenza Sentinel Surveillance System (SISSS) and the Portuguese Rede Médicos-Sentinela [16-18] (Table 1).

TABLE 1. Country-specific influenza vaccination programmes and influenza surveillance systems, the Netherlands, Portugal and Spain, influenza seasons 2015/16–2017/18

Characteristics	Netherlands	Portugal	Spain
Vaccination programme			
Vaccine used		Inactivated trivalent vaccine	
Target population	Population ≥ 60 years and medical risk groups (≥ 6 months-old)	Population ≥ 65 years and medical risk groups (≥ 6 months-old)	Population ≥ 65 years and medical risk groups (≥ 6 months-old)
Payment	Free of charge for the target groups	Free of charge for those ≥ 65 years in public primary care units	Free of charge for target groups
Place of vaccination	Uptake via GPs	Uptake at pharmacy or healthcare units	Uptake mainly in public primary care units, but also in hospitals if needed, and in occupational risk units of public and private organisations
ILI surveillance system			
Surveillance network	Nivel Primary Care Database – Sentinel Practices Weekly notification by sentinel GPs of cases meeting the ‘Pel-criteria’ [42]: sudden onset of symptoms AND fever (at least 38 °C) AND at least one of the following symptoms: cough, rhinorrhoea, sore throat, frontal headache, retrosternal pain or myalgia. GPs are recommended to swab at least the first two ILI patients attending each week. <sup>a</sup>	Rede Médicos-Sentinela	Spanish Influenza Sentinel Surveillance System
ILI case ascertainment and swabbing for confirmation		Weekly notification by sentinel GPs of cases meeting the EU ILI case definition	Weekly notification by sentinel GPs of cases meeting the EU ILI case definition [43]. GPs are recommended to swab the first two patients attending each week.
Laboratory confirmation of influenza	RT-PCR testing of nasopharyngeal/nose and throat swabs for influenza confirmation. If the test is positive for influenza, further tests are performed to determine virus type/subtype/lineage.		
Method of estimating positivity rate	Number of positive influenza detections among the swabbed respiratory samples × (1/sensitivity of RT-PCR); Sensitivity of RT-PCR = 0.95	Number of positive influenza detections among the swabbed respiratory samples	

## Vaccine coverage

In the Netherlands, influenza VC in the population aged 65 and older was estimated using pseudo-anonymised data from electronic medical files of GPs participating in the Nivel Primary Care Database [19]. The VC point estimate as well as 95% confidence intervals (CI) were computed using multilevel logistic regression, taking into account the clustering of patients in GP practices [19]. In Spain, VC in the population aged 65 and older was provided by the Spanish Ministry of Health, based on administrative data of the number of doses of influenza vaccine administered [20]. In Portugal, VC was estimated using data from the 2015/16 and 2016/17 waves of a population-based telephone survey among the non-institutionalised population in mainland Portugal [21].

## Vaccine effectiveness

We used the IVE among those aged 65 years and older estimated in the I-MOVE+ multicentre primary care-based test-negative design case-control study [22-24]. We pooled the VE of three seasons (2015/16–2017/18) (Supplementary Table S1) and weighted the (sub)type-specific VE by the proportion of influenza (sub)type detected in primary care settings in each country.

## Uncertainty estimation

To estimate the 95% CI for NAE and PF, we used a probabilistic Monte Carlo approach. We constructed empirical distributions for influenza-associated outcomes, positivity rate, IVE and VC and used the 2.5 and 97.5 percentiles of these empirical distributions to compute the 95% CI for NAE and PF. All analyses were performed using STATA software.

## Ethical statement

The study was based on aggregated data obtained from official statistics, influenza surveillance systems and epidemiological studies (IVE studies) with scientific protocols approved by the national ethical committees of the three involved countries. Given the ecological nature of the study, no additional ethical approval was required.

# Results

## Input data

### Medically attended influenza-confirmed cases at primary care level

In seasons 2015/16 and 2016/17, ILI epidemics occurred in similar periods in the three countries. In the 2017/18 season, a longer ILI epidemic was observed in the Netherlands (Supplementary Figure S1).

In all countries, the largest proportion of viruses detected in the sentinel networks were influenza A(H1N1)pdm09 in 2015/16, influenza A(H3N2) in 2016/17 and influenza B in 2017/18 (Table 2). The highest number of MAICC occurred in 2016/17 and 2017/18.

TABLE 2. Number of ILI, positivity rate and proportion of influenza (sub)types, MAICC, VC and VE among those aged  $\geq 65$  years, Portugal, Spain and the Netherlands, influenza seasons 2015/16–2017/18

	2015/16		2016/17		2017/18	
	n or %	95% CI	n or %	95% CI	n or %	95% CI
<b>Portugal</b>						
ILI (n)	9,161	6,656–12,297	21,646	17,289–26,766	12,366	9,340–16,057
Positivity rate (%)	27.8	20.5–35.1	47.4	40.2–54.5	46.2	43.0–49.3
MAICC (n)	2,547	1,641–3,686	10,261	7,673–13,087	5,708	4,247–7,298
VC (%)	50.1	42.1–58.1	57.5	50.8–64.1	60.8	55.5–65.9
Subtype A(H1N1)pdm09 (%)	90.4		0.2		20.0	
Subtype A(H3N2) (%)	1.3		99.6		14.0	
Type B (%)	8.3		0.2		66.0	
IVE (%)	40.6	22.6–58.6	8.5	–10.9 to 27.9	23.8	10.9–36.8
<b>Spain</b>						
ILI (n)	53,534	49,994–57,199	82,602	78,086–87,249	102,839	97,785–107,959
Positivity rate (%)	41.8	36.4–47.2	47.8	42.8–52.8	60.5	56.1–64.8
MAICC (n)	22,349	19,146–25,611	39,422	34,874–44,206	62,113	56,900–67,575
VC <sup>a</sup> (%)	56.1		55.5		55.7	
Subtype A(H1N1)pdm09 (%)	69.9		0.0		7.6	
Subtype A(H3N2) (%)	4.0		94.4		25.3	
Type B (%)	23.9		0.6		64.9	
IVE (%)	34.0	18.5–48.4	9.0	–10.8 to 27.8	20.0	8.8–30.5
<b>Netherlands</b>						
ILI (n)	73,250	63,890–83,290	86,700	76,530–97,650	96,300	86,120–106,900
Positivity rate <sup>b</sup> (%)	34.9	26.3–44.8	38.5	28.6–49.7	67.2	58.2–77.0
MAICC (n)	25,900	15,510–37,740	33,760	20,570–48,840	65,120	48,100–80,770
VC (%)	66.5	59.3–73.1	62.9	56.1–69.2	60.4	53.9–66.5
Subtype A(H1N1)pdm09 (%)	73.5		1.8		2.8	
Subtype A(H3N2) (%)	0.0		92.9		18.3	
Type B (%)	26.5		5.4		78.9	
IVE (%)	37.1	21.7–52.5	9.7	–8.4 to 27.8	19.5	4.7–34.4

#### Vaccine coverage

In the study period, VC in the population aged 65 years and older ranged between 50.1% (Portugal) and 66.5% (the Netherlands) (Table 2). The VC increased in Portugal (from 50.1% in 2015/16 to 60.8% in 2017/18), decreased in the Netherlands (from 66.5% in 2015/16 to 60.4% in 2017/18) and remained similar in Spain.

### Influenza vaccine effectiveness

The IVE estimates ranged between 34.0% and 40.6% in 2015/16, 8.5% and 9.7% in 2016/17, and 19.5% and 23.8% in 2017/18 (Table 2). In the 2016/17 season, when influenza A(H3N2) virus was circulating in all countries, the IVE among the population 65 years and older was notably lower compared with other seasons.

### Impact of influenza vaccination in the prevention of medically attended influenza-confirmed cases

#### Number of averted events

Among those aged 65 years and older, influenza vaccination prevented an average per season of 715 MAICC in Portugal, 5,042 in Spain, and 6,457 in the Netherlands (Table 3). In Portugal, Spain and the Netherlands, the NAE per 100,000 population 65 years and older was 30, 61 and 275 in the 2015/16 season, 24, 24 and 69 in the 2016/17 season and 44, 88 and 268 in the 2017/18 season, respectively. The three seasons' NAE rate was 204 cases per 100,000 in the Netherlands, 58 cases per 100,000 in Spain and 33 cases per 100,000 in Portugal (Table 3).

#### Prevented fraction and number needed to vaccinate

The seasonal average estimates of MAICC prevented fractions were similar for the three countries. The PF ranged between 19.1% and 24.7%, in the 2015/16 season, between 4.9% and 6.1% in 2016/17 and between 11.1% and 14.5% in 2017/18 (Table 3).

As expected, the number needed to vaccinate to prevent one MAICC followed the pattern observed for NAE, with the lowest NNV values for season 2017/18 and the highest for season 2016/17 in all countries (Supplementary Table S2).

TABLE 3. Seasonal average, number and rates of MAICC events averted among those aged  $\geq 65$  years, by season, Portugal, Spain and the Netherlands, influenza seasons 2015/16–2017/18

Country	Indicator	2015/16	2016/17 <sup>a</sup>	2017/18	Average
Portugal	NAE (95% CI)	650 (265–1,162)	527 (–746 to 1,876)	967 (316–1,701)	715 (215–1,246)
	Rate NAE/10 <sup>5</sup> (95% CI)	30 (13–52)	24 (–35 to 85)	44 (15–77)	33 (9.9–57.3)
	PF in % (95% CI)	20.3 (10.7–28.4)	4.9 (–7.9 to 15.1)	14.5 (5.4–21.9)	10.7 (3.3–16.4)
Spain	NAE (95% CI)	5,268 (2,453–8,224)	2,073 (–2,657 to 6,758)	7,787 (2,891–12,648)	5,042 (2,602–7,500)
	Rate NAE/10 <sup>5</sup> (95% CI)	61 (29–96)	24 (–30 to 78)	88 (33–143)	58 (30–86)
	PF in % (95% CI)	19.1 (10.1–26.4)	5.0 (–7.1 to 14.5)	11.1 (4.4–16.9)	10.9 (5.9–15.3)
Netherlands	NAE (95% CI)	8,483 (3,396–16,255)	2,194 (–2,141 to 7,524)	8,694 (1,158–17,487)	6,457 (2,310–12,013)
	Rate NAE/10 <sup>5</sup> (95% CI)	275 (110–527)	69 (–68 to 238)	268 (36–540)	204 (74–380)
	PF in % (95% CI)	24.7 (12.7–34.6)	6.1 (–6.7 to 16.8)	11.8 (1.8–20.3)	14.2 (5.2–21.5)

## Discussion

Our results suggest that during the 2015/16 to 2017/18 seasons, the influenza vaccination programmes in Portugal, Spain and the Netherlands had a sustained and positive impact on primary care MAICC in the population aged 65 years and older. The influenza vaccination programmes prevented an annual average of 33–204 primary care MAICC per 100,000 and 10.7–14.2% of potential MAICC that would have occurred without vaccination programme.

The impact of the influenza vaccination programmes varied across the influenza seasons. We obtained MAICC prevented fractions in the 2015/16 season of 19.1–24.7%, comparable to a study conducted in the United States (US) in 2013 that reported an average prevented fraction of 18.4% over six seasons [11].

We observed the lowest NAE during the 2016/17 season, when influenza A(H3N2) dominated in all countries. Given that VC did not vary considerably in the three seasons, the main drivers for the differences in season-specific NAE would be the number of MAICC and the IVE estimates. Seasons with dominant influenza A(H3N2) circulation are reported to produce a high influenza burden in the elderly population [25], and often a limited IVE against subtype A(H3N2) [26,27]. In 2016/17, the IVE was below 10% in the three countries. Despite this low protection, our results suggest that influenza vaccination programmes averted 24, 24 and 69 primary care MAICC per 100,000 population among those aged 65 years and older in Portugal, Spain and the Netherlands, respectively. This is consistent with other studies where, even in seasons with low vaccine effectiveness, the vaccination programme was able to avert influenza consultations, hospitalisations and deaths [2,9,28]. Particularly for the influenza vaccine with often limited effectiveness [26,29], such a message might illustrate considerable vaccine impact at population level, even when the vaccine effect at individual level is suboptimal.

Also the prevented proportion of primary care MAICC was the lowest in the 2016/17 season, namely 4.9% in Portugal, 5.0% in Spain and 6.1% in the Netherlands. A similar low PF (7–11%) was estimated in the US for seasons with predominant influenza A(H3N2) circulation [30,31]. The NAE results also differed by country, with Spain and Portugal both showing lower estimates than the Netherlands. As NAE is a linear function of primary care MAICC, a large difference in MAICC across countries or across seasons will lead to a large NAE difference.

In this study, we estimated the MAICC using primary care surveillance data. Potential explanations for the observed differences could be (i) the influenza positivity rate, (ii) the methods of the surveillance system, e.g. the case definition used to recruit ILI cases from the health system and (iii) the healthcare seeking behaviour.

The percentage of positive influenza cases among all tested varies between seasons and between countries, depending mainly on the (sub)type of the circulating virus and the sentinel GPs' swabbing practice. The positivity pattern in the three countries was similar, with the highest positivity rate in the 2017/18 season, when influenza B virus accounted for more than 65%. The opposite was observed in 2016/17, when almost all isolates were influenza A(H3N2). This subtype is more frequent among older adults in whom ILI rates are generally lower [32], which could explain a lower positivity rate.

Differences among countries can be derived from different (sub)type distributions in the circulating virus and also from different real swabbing practices between countries, even if, as in our study, systematic swabbing is established in the three countries. Another source of differences is the correction of the Dutch positivity rate for the RT-PCR sensitivity. Given that the RT-PCR sensitivity rate used was 95%, this would represent a systematic relative increase of 5.3% ( $1/0.95$ ) in the Dutch positivity rates. This small increase does not explain the different NAE rate between countries.

Differences in national surveillance protocols may also play a role, e.g. the ILI case definition: In the Netherlands, the ILI case definition requires a fever  $\geq 38^{\circ}\text{C}$ , while the EU ILI case definition used in Spain and Portugal only requires 'fever or feverishness'. Fever may be associated with more severe illness and with a higher likelihood of healthcare use [33,34]. In addition, the identification of ILI patients and the selection of patients for swabbing rely on the GP's criteria, which may be influenced by how influenza surveillance has been done historically in their country, regardless of the ILI case definition used. Another important factor contributing to the different MAICC is probably the healthcare seeking behaviour in the age group 65 years and older. The use of primary healthcare has been described to be the highest in the Netherlands among the three countries [35]. In Portugal, the general population often uses emergency rooms at hospitals to treat acute illness [36], while in Spain and the Netherlands, the GP is the first point of call for an influenza consultation [37,38].

This study has limitations. One is the approach used to measure the impact assuming no indirect effect, i.e. no herd protection conferred by the vaccinated population to the non-vaccinated population. Dynamic model simulations have demonstrated that the indirect effect may not be negligible, particularly regarding the effect of vaccinating children on the adult population [39,40]. A meta-analysis revealed that influenza vaccination in children may result in herd protection for the community-dwelling elderly population against influenza-associated mortality [41]. However, to observe this herd protection in the population aged 65 years and older, a minimum VC of 20% is needed in children [39]. In our study, the indirect effect may be small since there is no overall vaccination recommendation for the younger population in any of the three countries and VC in adults younger than 65 years is presumably low. In Portugal

for instance, the VC in all three seasons was below 5% in the 0–15 year-olds and between 7% and 18% in adults younger than 65 years [21]. In the Netherlands VC was 10% for the total population aged 18–64 years in the 2017/18 season [19]. However, non-vaccinated elderly people may still benefit from vaccination of younger age groups, particularly in settings with high VC in those 65 years and older [39]. As such, the NAE estimated in this study may be underestimated and the real impact of the vaccination programme could be even higher.

Another component that is not accounted for in our approach is that part of the estimated impact outcome measures may be attributable to previously acquired immunity, either through vaccination or natural infection. Our method does not allow us to distinguish which proportion among the prevented fraction is due to previous immunity and which is due to the current seasonal vaccination.

Another limitation to be acknowledged are the different ILI definitions and sources to estimate the VC, where some countries used population-based surveys, others GP surveys or administrative registries. In Portugal and the Netherlands, only the VC of community-dwelling elderly population is captured.

In Spain, regional administrative registries were used to calculate the national influenza VC. In the majority of the regions, the registry includes vaccines administered in both the public and the private sector. Only a few small regions report only vaccines administered in the public sector, therefore, we expect that influenza VC used reflected the VC in the population.

The study has several noteworthy strengths. Firstly, we used population-based surveillance data, so that the study can be replicated in several seasons and the results generalised for the population. Secondly, the IVE estimates derived from European pooled estimates were specific to the influenza (sub)type and adjusted to virus circulation in the country. This procedure not only allows us to obtain more precise estimates but also increases the robustness of the NAE results. Finally, we used country-specific data for all three countries individually, with harmonised analytical methods and definitions, allowing direct inter-country comparison.

## **Conclusion**

The development of the common protocol resulted in a comparable population-based indicator of the impact of influenza vaccination programmes in the three countries. This can benefit existing influenza surveillance systems which already capture the annual influenza burden through national surveillance as well as estimation of the IVE through the I-MOVE network. Furthermore, by including severe influenza outcomes in future impact estimations, such as hospitalisations and deaths related to influenza, we will be able to provide a comprehensive view of the annual burden of influenza-related morbidity and mortality averted by vaccination.

These results are important to support public health communication aiming to increase VC in high-risk groups. Influenza vaccination programmes can gain impact by increasing VC and/or IVE. Quantifying the benefit of annual vaccinations through estimates of their impact may contribute to this public health challenge, which could be a key message to the general public and decision makers, particularly in seasons with low vaccine effectiveness.

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### Authors' contributions

All authors contributed to development of the protocol. Ausenda Machado, Clara Mazagatos and Frederika Dijkstra coordinated the data gathering, analysis for each country and writing the first draft. Irina Kislaya, Alin Gherasim, Scott McDonald, Esther Kissling, Adam Meijer and Mariëtte Hooiveld contributed data gathering and analysis. Marta Valenciano, Baltazar Nunes and Amparo Larrauri coordinated the impact study. All authors contributed to interpretation and read and revised the final article.

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## Supplementary material

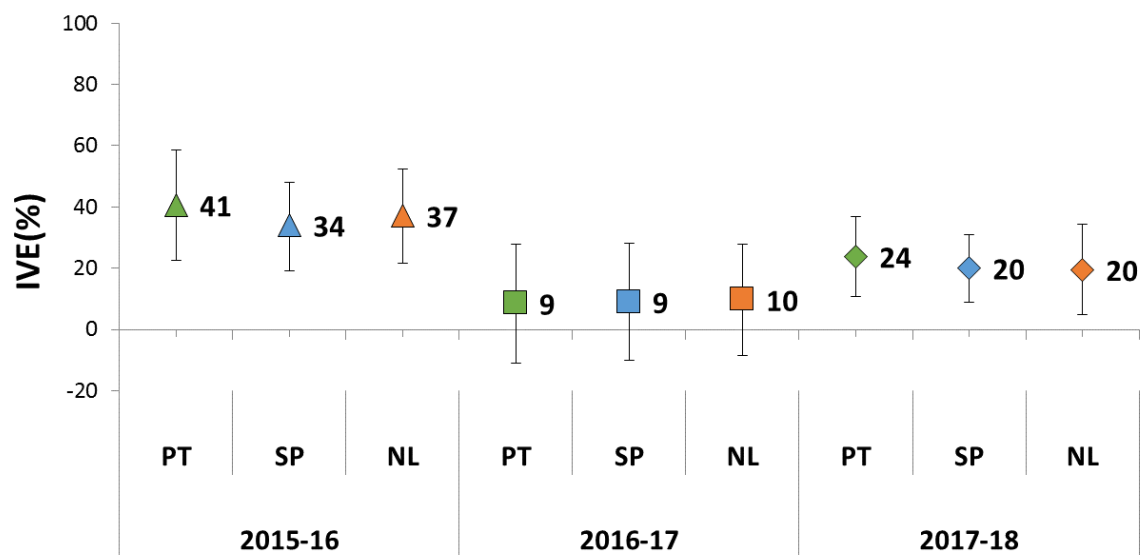
This supplementary material is hosted by Eurosurveillance as supporting information alongside the article **Impact on primary care of influenza vaccination programmes among the elderly population in Portugal, Spain and the Netherlands: 2015/16 to 2017/2018 influenza seasons** on behalf of the authors who remain responsible for the accuracy and appropriateness of the content. The same standards for ethics, copyright, attributions and permissions as for the article apply. Eurosurveillance is not responsible for the maintenance of any links or email addresses provided therein.

**Table S1. Pooled type/subtyped IVE resulted from the I-MOVE+ multicenter primary care based study**

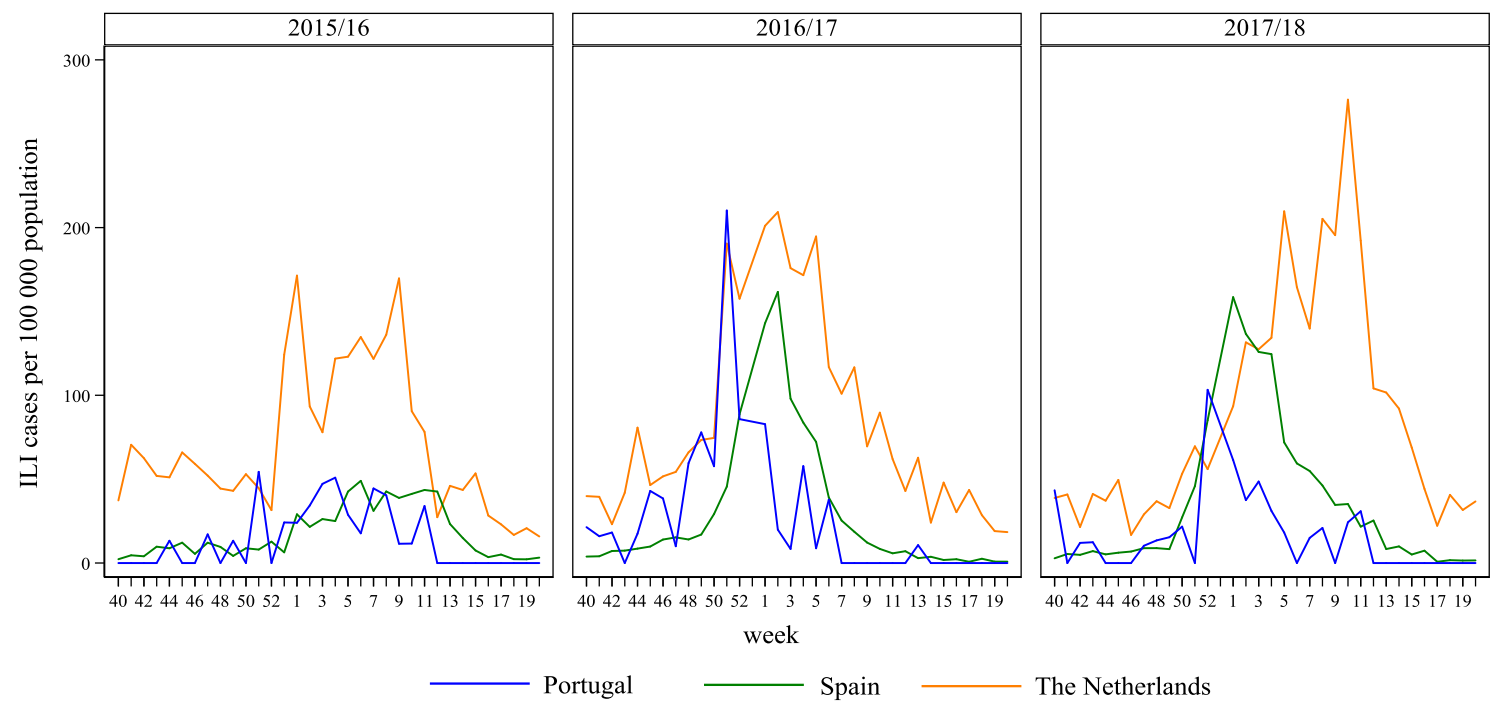
Type/subtype	Seasons included	VE (95% CI)
A(H1N1)pdm09	2015/16-2017/18	42.8 (19.6; 59.3)
A(H3N2)	2016/17-2017/18	8.4 (-13.1; 25.8)

<b>B</b>	2015/16-2017/18	21.3 (0.9; 37.5)
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**Figure S2. Influenza vaccine effectiveness against medically-attended confirmed influenza among those aged 65 years and older by influenza season in Portugal, Spain and the Netherlands. Influenza seasons 2015-16 to 2017-18**



**Figure S1. Influenza Like Illness rates among the population aged 65 years and older, in Portugal, Spain and the Netherlands in seasons 2015/16 to 2017/18**





## **Impact of national influenza vaccination strategy in severe influenza outcomes among the high-risk Portuguese population**

Ausenda Machado<sup>1,2</sup>, Irina Kislaya<sup>1,2</sup>, Amparo Larrauri<sup>3</sup>, Carlos Matias Dias<sup>1,2</sup>, Baltazar Nunes<sup>1,2</sup>

1 – Departamento de Epidemiologia, Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa, Portugal

2 - NOVA National School of Public Health, Public Health Research Centre, Universidade NOVA de Lisboa, Lisbon, Portugal

3 - National Centre of Epidemiology, Institute of Health Carlos III. CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

### **Abstract**

#### **Background**

All aged individuals with a chronic condition and those with 65 and more years are at increased risk of severe influenza post-infection complications. There is limited research on cases averted by the yearly vaccination programs in high-risk individuals. The objective was to estimate the impact of trivalent seasonal influenza vaccination on averted hospitalizations and death among the high-risk population in Portugal.

#### **Methods**

The impact of trivalent seasonal influenza vaccination was estimated using vaccine coverage, vaccine effectiveness and the number of influenza-related hospitalizations and deaths. The number of averted events (NAE), prevented fraction (PF) and number needed to vaccinate (NVN) were estimated for seasons 2014/15 to 2016/17.

#### **Results**

The vaccination strategy averted on average approximately 1833 hospitalizations and 383 deaths per season. Highest NAE was observed in the  $\geq 65$  years population (85% of hospitalizations and 95% deaths) and in the 2016/17 season (1957 hospitalizations and 439 deaths). On average, seasonal vaccination prevented 21% of hospitalizations in the population aged 65 and more, and 18.5% in the population with chronic conditions. The vaccination also prevented 29% and 19.5% of deaths in each group of the high-risk population. It would be needed to vaccinate 3,360 high-risk individuals, to prevent one hospitalization and 60,471 high-risk individuals to prevent one death.

#### **Conclusion**

The yearly influenza vaccination campaigns had a sustained positive benefit for the high-risk population, reducing hospitalizations and deaths. These results can support public health plans toward increased vaccine coverage in high-risk groups.

### **Background**



The annual circulation of influenza virus causes epidemics that can lead to a considerable burden of hospitalization and death, especially for a sub-group of the population with a high risk of influenza complications. It has been estimated that annually influenza is responsible for an excess of respiratory deaths that ranged from 4.0 to 8.8 per 100,000 worldwide, and these figures increased with age, causing an excess of 2.9 to 44.0 per 100 000 individuals in the 65 to 74 age group (1). In Portugal, influenza burden patterns are similar, and in the all-age population, influenza epidemics have been estimated to be associated with an average of 24.7 all-cause excess deaths per 100,000 (2) and 19.4 per 100,000 excess pneumonia and influenza hospitalizations (3).

Besides age, the presence of certain medical conditions, namely diabetes, obesity, immunodeficiency and chronic respiratory, cardiovascular, kidney and renal diseases, are well-established risk factors for severe influenza complications such as hospitalizations, intensive care and death (4).

In Portugal, an at-risk based vaccination program has been in place at least since 2001/2002. In accordance with the National Directorate for Health clinical guidelines (5), influenza vaccination is strongly recommended to those at higher risk for influenza complications (chronic and immunocompromised patients older than 6 months of age, pregnant women), as well as those aged 65 and over and to institutionalized to whom the vaccine is offered free of charge. Seasonal influenza vaccination is also recommended to health professionals and other caregivers.

Every year seasonal influenza vaccination campaigns with inactivated trivalent vaccine start in early October run throughout the fall and winter. Despite gradual increase in influenza vaccine uptake in the 65 years and older population (6), in Portugal, like in most other European Union (EU), vaccination coverage (VC) still has not reached the target of 75% set by the World Health Organization and the European Commission (EC) (7). Individuals with chronic conditions have even lower seasonal influenza vaccine coverage's, that ranged between 32.3% in 2015/16 and 41.0% in the 2017/18 season (8).

To increase the acceptability of the vaccine, it is important to quantify the benefits of annual influenza vaccination, namely by estimating its impact at the population level. Influenza vaccine effectiveness (IVE) studies are conducted in Europe every season and allow early and end of season estimates on the reduction of medically attended confirmed influenza infections, either at primary care or hospital level (9–11). However, population data on influenza-associated outcomes prevented each season by influenza vaccination, in high-risk populations, is scarce. Moreover, measuring the impact of the influenza vaccination strategy every season is methodologically challenging, as influenza vaccination programmes are in place for several decades, which inhibit the before/after comparison of the introduction of this public health intervention. To overcome this, some authors use an ecologic approach that permits the estimation of influenza vaccination impact using data on vaccine coverage, vaccine effectiveness and the number of observed influenza events (12–16).

This study aimed to estimate, the influenza-related hospitalizations and intra-hospital deaths attributable to influenza averted by seasonal influenza vaccination strategy, during the influenza seasons 2014/15 to 2016/17, in individuals 65 years and older and those, at any age, with comorbidity that represents a high risk group for influenza complications.

## **Methods**

### *Hospitalization data*

We developed an observational retrospective ecologic study using the National Hospital Discharge Database.

This database covers all public hospitals in Portugal mainland and includes demographic data, diagnosis, procedures, length of stay and discharge outcomes for all episodes of hospital care. In the 2006-2016 period, this database included approximately 79% of all hospital admissions that occurred in Portugal (17). Diagnoses and some procedures (laboratory results not included) are coded using the International Classification of Diseases (ICD) - 9th Revision Clinical Modification (ICD-9-CM) version (18) until 1st January 2016 and ICD-10-CM (19) onwards. Final validated databases are available for research after every 9 to 12 months.

#### *Study population*

The target population of this study is high-risk individuals, namely, aged 65 and older or <65 years with a chronic condition (diabetes, chronic respiratory, cardiovascular, kidney and renal diseases, obesity, immunodeficiency) for which the influenza vaccine is recommended (20–22). An individual was considered as having a chronic condition if it was hospitalized and had a secondary diagnosis within a set of chronic conditions presented in Table 1.

To estimate the number of high-risk individuals in Portugal, we used the population estimates from the national statistical office (Statistics Portugal) (23) and the proportion of self-reported chronic conditions in the 0-4 and 15-64 age groups from two health surveys representative at National and regional level (24,25).

#### *Severe influenza-related events*

We considered two severe influenza-related outcomes: hospitalizations (admissions for >24 hours) and intra-hospital deaths attributable to influenza.

#### *Hospitalizations*

Hospital admissions due to influenza were obtained by multiplying the weekly number of severe acute influenza respiratory illness (SARI) hospitalizations by the weekly proportion of SARI influenza positivity. The proportion of influenza-positive was obtained from the hospital-based Portuguese laboratory network for the diagnosis of influenza (26).

A SARI hospitalization was defined as an episode with hospital stay length higher than 24 hours with a primary diagnosis coded as any of SARI codes defined in Integrated Monitoring of Vaccines Effects in Europe (I-MOVE+) protocol (27) (Table 2).

#### *Deaths*

Intra-hospital deaths attributable to influenza (from this point forward designated as deaths) were estimated using the hospital discharge outcome information. The number of deaths that occurred in patients hospitalized with SARI diagnosis during the study period was multiplied by the proportion of influenza-positive, obtained from the Portuguese laboratory network for the diagnosis of influenza (26).

#### *Study period*

The impact of the influenza vaccine national program was estimated for three seasons, 2014/15, 2015/2016 and 2016/17. For each season the analysis was restricted to the epidemic periods. Epidemic periods were established by the primary care-based Portuguese sentinel influenza surveillance system (Table 3). For each season, the study period comprises the epidemic periods, plus 3 weeks lag as more severe outcomes are expected to occur with delay.

#### *Number of averted severe influenza-related events prevented fraction*

To assess the annual impact of the influenza vaccination programmes we estimated the number of severe influenza-related events (IRE) among the high-risk population averted by vaccination (NAE), the respective disease prevented fraction (PF) and the number of high-risk individuals in the population needed to be vaccinated to avoid one IRE (NNV).

NAE measures the impact of the vaccination program in absolute terms and represents the difference between observed IRE (n) and IRE expected in the absence of the vaccination program (N) and was estimated as:

$$NAE = N - n = n \cdot (IVE \cdot VC) / (1 - (VC \cdot IVE))$$

where  $n$  – observed IRE,  $IVE$  – Influenza vaccine effectiveness,  $VC$  – vaccine coverage (details on the formula available at Additional file 1) .

The PF, estimated as  $PF = NAE / (n + NAE)$ , measures the impact of vaccination in relative terms and represents the proportion of averted IRE out of the number of IRE in the population without influenza vaccination program (12–14,16,28).

The number needed to vaccinate was also computed as:

$$NNV = 1 / (IVE \cdot N / \text{Population}).$$

#### *Vaccine coverage (VC)*

The influenza vaccination coverage was estimated using the influenza vaccine coverage monitoring system (6,29), a population-based survey of a sample of approximately 1000 households from Portugal mainland, selected using random digit dialling of mobile and landline phones. In each household, one individual aged 18 or more is interviewed providing information on his/her vaccination status and the vaccination status of the other household elements. The questionnaire also includes information on chronic conditions. Vaccine coverage was estimated for the population with conditions for which the vaccine is recommended and for the population aged 65 and more years.

#### *Influenza Vaccine effectiveness (IVE)*

We used hospital-based meta-analysis type/subtype IVE estimates. IVE among those aged 65 and older and with less than 65 years (30) were weighted by the distribution of circulating influenza type/subtypes virus in each season in Portugal. Reported match/unmatched vaccine information (30) was considered. Data on circulating influenza type/subtypes detected in the hospital settings were obtained from the Portuguese Hospital laboratory network for the influenza diagnosis (26,31).

Vaccine effectiveness against intra-hospital deaths of 56% [14% to 77%] reported by Casado et al. (32) for the Spanish population was used for all high-risk groups.

#### *Uncertainty*

To estimate 95% confidence intervals for NAE, NNV, and PF we used Monte Carlo simulations (more detail on Additional file 2). We assumed a Poisson distribution for the number of influenza-related events and Normal distributions for  $\log(1-IVE)$  and  $\log(VC/(1-VC))$  (13). The distributions parameters were derived from respective point estimates and 95% confidence intervals. We drew 10 000 simulations samples of influenza-related events, IVE and VC to obtain empirical distributions of NAE, NNV, and PF in each season and average across three seasons. We used the 2.5 and 97.5 percentiles of these empirical distributions as lower and upper limits of the 95% confidence intervals.

Table 1. List of International Classification of Diseases (ICD) 9th and 10th version codes for chronic conditions

	ICD 9th version	ICD 10th version
Respiratory	011, 490–511, 512.8, 513–517, 518.3, 518.8, 519.9, 714.81	A15, J40-47, J60-94, J96, J99, J182, M34.81, M05.10
Cardiovascular	746.9 402.0-402.91	Q24.9 I11.0-I11.9

	428.42, 412,0-412,9, 414.9	428.32, 413.0-413.9,	482.22 150.22, 150.32, 150.42 125.2, 120.8, 120.1, 120.9, 125.0-125.9 414.9
Renal	581.0-581-9, 585.0-585.9		N18, N04
Kidney	571.0-571.9 576.2		K70, K74, K72.1
Hematologic	282.4, 282.5, 282.6		D56, D57
Imunocompromised	042, 279, V08, V42		B20, D80-84, D89.8-9, Z21, Z94
Diabetes mellitus	250		E10-11; Z94.0-Z94.4, Z94.6-Z94.9
Genetic conditions	273.4		E88.01
Obesity	278.00, 278.01, 278.03		E66.01, E66.2, E66.9

ICD International Classification of Diseases (ICD)

## Results

We estimate that during the study period there were about 3.82 million high-risk individuals in Portugal targeted by the National vaccination program: 2.07million were aged 65 and more and about 1.75 million aged less than 65 years and had a chronic condition for which the influenza vaccine is recommended.

During the study period, the estimated number of SARI hospitalizations among high-risk individuals ranged from 21955 (season 2016/17) to 29099 (season 2014/15) (Table 3). Influenza deaths varied between 778 in season 2015/16 and 1134 in season 2014/15.

The most frequent comorbidities of hospitalized SARI patients were chronic respiratory diseases (46%), followed by diabetes (32%) and cardiovascular diseases (24%). The highest number of influenza-related hospitalizations and deaths was estimated in season 2014/15, a B/Yamagata dominant season but with A(H3N2) circulation (7946 hospitalizations and 1134 deaths). Influenza vaccine effectiveness was lower in the 2014/15 season than in the other seasons. Overall, point estimate IVE was lower in the individuals aged 65 and more years than in younger individuals with chronic conditions. In contrast, vaccine coverage was higher in the older population, increasing from 49.8% in the 2014/15 season to 57.5% in the 2016/17 season.

On average, per season, the influenza vaccination campaign averted approximately 1833 hospitalizations and 383 deaths in the Portuguese high-risk population (Table 4). The highest number of averted events occurred in the population aged 65 and more years and the 2016/17 season, a season with a predominance of A(H3N2) virus.

Overall, the vaccination strategy prevented on average, 21% and 18.5% of influenza hospitalizations in those 65 years and older and under 65 years with chronic conditions, respectively, and 19.5% and 37.4% of deaths in the <65 years and in the older adult population, respectively. To prevent one influenza-related hospitalization or death, we would need to vaccinate on average 3360 and 60471 high-risk individuals, respectively.

Table 3. Distribution per season of the number of severe acute respiratory infections (SARI) hospitalizations and deaths, SARI Influenza-related hospitalizations and deaths, influenza vaccine effectiveness and vaccine coverage estimates for  $\geq 65$  years and <65 years with a chronic condition.

<b>Season features</b>	<b>2014/15</b>	<b>2015/16</b>	<b>2016/17</b>
<b>Epidemic period</b>	w1 to w7/2015	w53/2015 to w7/2016	w48/2016 to w1/2017
<b>Dominant type/subtype</b>	B/Yam	AH1N1pdm09	AH3
<b>SARI Hospitalizations</b>			
≥65 years (n)	24720	21913	18724
Chronic condition (n)	4379	4595	3231
<b>SARI deaths</b>			
≥65 years (n)	3824	3044	2942
< 65 years with a chronic condition (n)	198	196	137
<b>Influenza hospitalizations</b>			
≥65 years	6742	5107	6003
<65 years with a chronic condition	1204	1069	1031
<b>Influenza deaths</b>			
≥65 years	1078	731	909
<65 years with a chronic condition	56	47	42
<b>Influenza vaccine effectiveness (IVE %)</b>			
≥65 years[ 95%CI]	29.0[14.7 to 43.4]	49.1[26.4 to 71.7]	42.9[33.0 to 52.8]
<65 years [ 95%CI]	46.1[20.9 to 71.3]	53.0[34.9 to 71.1]	58.9[38.1 to 79.6]
<b>Vaccine coverage (VC %)</b>			
≥65 years[95%CI]	49.8[41.3 to 58.4]	50.1 [42.1 to 58.1]	57.5 [50.8 to 64.1]
Chronic condition [95%CI]	34.2 [28.1 to 40.9]	32.3 [26.8 to 38.4]	39.7 [33.7 to 45.9]

*SARI- severe acute respiratory infections; w- week; IVE- influenza vaccine effectiveness; CI- confidence intervals; VC- vaccine coverage*

Table 4. Estimates of the annual average and seasonal prevented fraction and number of averted influenza hospitalizations and deaths attributed to the vaccine program, for seasons 2014/15 to 2016/17.

IRE	Season			
	2014/15	2015/16	2016/17	Average
<b>Hospitalization</b>				
<i>≥65 years</i>				
NAE (n) [95%CI]	1124 [443-1863]	1644 [460-2799]	1957 [1326-2657]	1584 [1058-2097]
PF (%) [95%CI]	14.3 [6.2-21.6]	24.3 [8.2-35.4]	24.6 [18.1-30.7]	21.0 [15.1-26.1]
NNV (n) [[95%CI]	890 [565-2233]	621 [384-2050]	616 [473-882]	741 [553- 1426]
<i>&lt;65 years with chronic condition</i>				
NAE (n) [95%CI]	222 [42-383]	218 [106-326]	311 [135- 473]	249 [158-337]
PF (%) [95%CI]	15.6 [3.3-24.1]	16.9 [9.1-23.4]	23.2 [11.6-31.5]	18.5 [12.5-23.4]
NNV (n) [[95%CI]	2657 [1628- 10924]	2564 [1857-5172]	2200 [1540 - 4957]	2619 [1921 - 6015]
<b>Deaths</b>				
<i>≥65 years</i>				
NAE (n) [95%CI]	409 [81-721]	281 [52-489]	427 [95-743]	371 [198-541]
PF (%) [95%CI]	27.7 [7.0-40.1]	27.5 [6.7-40.1]	31.9 [9.4-45.0]	29.0 [18.0-37.4]
NNV (n) [[95%CI]	2416 [1459-10267]	3613 [2166-15078]	2796 [1633-10422]	3241 [1845-10141]
<i>&lt;65 years with chronic condition</i>				
NAE (n) [95%CI]	13 [3-22]	10 [2-49]	12 [3-20]	12 [6-16]
PF (%) [95%CI]	18.9 [4.8-27.9]	17.9 [4.3-26.1]	22.0 [6.5-31.7]	19.5 [11.8-25.4]
NNV (n) [[95%CI]	45211 [29413-176520]	54149 [35348-205119]	58216 [37146-206237]	57230 [37610-176457]

IRE- influenza related event; NAE- number of averted events; CI- confidence interval; PF- prevented fraction; NNV- number needed to vaccinate

## Discussion

We estimated that during the influenza seasons 2014/15, 2015/16 and 2016/17, the trivalent inactivated seasonal influenza vaccination strategy averted each season, on average, more than 1830 hospitalizations and 380 deaths in the high-risk population in Portugal.

Overall, the impact of the program was higher in the population aged 65 and more years, a sub-group with higher VC but systematically lower IVE, in which it accounted for 86% and 95% of the total number of averted hospitalizations and deaths. These results reflect not only the higher risk of complication of that population but also the potential gain that could be achieved by increasing the vaccine coverage. In seasons with lower influenza vaccine, performance high vaccine coverage could balance and allow reasonable prevented fraction. Also, it demonstrate that, even with limited effectiveness, the influenza vaccination program prevented a considerable number of hospitalizations and deaths associated with influenza in the 65 years and older population.

The results also show that, even in seasons with a mismatch, between circulating virus and vaccine composition, like the 2014/15 season, vaccinating this high-risk group of individuals averted 1346 hospitalizations and 264 deaths. This included averting 5% premature deaths of individuals aged <65 years. The highest number of averted events occurred in the A(H3N2) dominant 2016/17 season, where approximately 2268 hospitalizations and 442 deaths were prevented. These results are important given that in seasons with A(H3N2) predominant circulation i) a considerable burden of influenza is observed in the target vaccination subgroup and ii) vaccine effectiveness tends to be low against this virus sub-type (30,33). Besides, in seasons with A(H3N2) predominance, the influenza vaccination impact is limited in preventing primary care consultations by influenza (34) and thus this result reinforces the main objective of the influenza vaccination strategy as the reduction of severe complications by influenza.

The estimated prevented fractions indicate that on average, per season, the influenza vaccination strategy prevented 21% of the hospitalization in the population aged 65 and more and 18.5% in the <65 years with a chronic condition. Season specific estimates in 2015/16 season (PF=24.3%) was comparable to estimates obtained in a study for the USA population for the same season (22.5%; 95%CI: 13.5-31.4) (35) and were also comparable to estimates reported for the USA population in other seasons with predominant circulation of A(H1)pdm09 virus (36). However, for the 2014/15 and 2016/17 season, our estimates were higher than the reported for the USA. For instance, it was double than the 7% estimates published for the 2014/15 season (15,37) and 11.5% estimates for the 2016/17 season (38). Considering that the PF mainly depends on the VC and IVE estimates (39) and that VC was comparable between countries and was stable along the period in study, the main contributor to the observed differences was most probably IVE. In our study, we used type/subtype specific meta-analysis estimates and weighed to account for the virus in circulation. In the 2014/15 season, although the mismatched A(H3N2) virus circulated in Portugal, the predominant virus was type B virus (40). As such, season-specific IVE for 2014/15 season was estimated to be 29% in the more than 65 years population and 46% in the ones with chronic conditions, thus justifying the increased estimated PF. In the 2016/17 season, the predominant A(H3N2) in Portugal matched the vaccine strain and this study final IVE estimates for the population aged 65 and more were considerably higher than the 17% published in Europe (41) and 20% in the USA (38).

Concerning the most severe outcome, we estimate that 19.5% or 29% of hospitalized influenza deaths were prevented by the vaccination strategy. The comparison with other studies is limited as most studies focus on older adults and all-cause mortality (16) or cause-specific mortality outcomes (13,15). Nevertheless, and though using a conservative estimate of 56% reduction of influenza-related intra-hospital deaths, we estimate that the vaccination strategy would prevent premature deaths in <65 years population with chronic conditions.

To prevent one hospitalization or death we would need to vaccinate additionally 3982 individuals aged 65 and more years and 59 849 individuals with chronic conditions. These

results indicate that there is a potential increased benefit if the 75% VC target would be achieved.

The results presented should be interpreted in light of the study's limitations. The ecologic nature of the study and the use of several data sources limits the study external validity.

In relation to the study design, the main objective of the study is to measure the impact of the influenza vaccination programme and this is methodologically challenging. For some infectious diseases, as pneumococcal pneumonia, the impact of vaccination in the older adult Portuguese population was measured by comparing hospitalizations rate before and after the introduction of the pneumococcal conjugated vaccines (42). However, for influenza vaccination, with a vaccination programme in place for long time, such approach is not feasible. The method that we used to estimate the influenza vaccination strategy impact has been used by several countries (12–16,28) and consists in evaluating how the vaccination programme works at population level, using as reference an hypothetical totally susceptible population that has never been exposed to the intervention.

The methods measure only the direct effect of vaccination in the population and thus represents a more conservative estimate of the impact as does not account for indirect effects. Also, there are some limitations to the data. First, hospitalization and deaths were retrieved from a hospital discharge database collected for administrative and hospital financing purposes, which covers approximately 79% of the national hospitalizations (17). Another limitation of this database to estimate the impact in each season is the time to have available data. The hospitals are in the process of changing from ICD9 to ICD10 and this has delayed obtaining the final database jeopardizing the use of annual estimation of vaccination strategy impact to prepare the next season. Finally, this database includes diagnoses and some procedures codes, however, laboratory results are not systematically done nor available which prohibit the use of influenza laboratory diagnoses directly from it. This limitation had as consequence the need of using an external database (from the hospital-based Portuguese laboratory network for the diagnosis of influenza) to obtain an estimate of the influenza hospitalized cases.

In our study, the VC was obtained from self-reported data and restricted to non-institutionalized Portuguese mainland residents. Given that VC is higher in the institutionalized population, our VC results may be underestimated and thus underestimation of impact results. Finally, IVE against mortality may not represent the Portuguese population, since we used VE derived from a study in a population from Spain that could have a different distribution of chronic conditions and access to health care. Also, the same estimate was used for all seasons and sub-group of population and IVE is expected to vary between seasons and in younger individuals.

The study has also considerable strengths. First, to our knowledge, this is the first attempt to measure the vaccination impact in a population <65 years with chronic conditions. Considering that this subgroup is targeted by influenza vaccination programs and is an important fraction of the population (26.2% of population aged 15-64 years) our results demonstrate important benefits by the seasonal vaccination in this sub-group. In a country with low seasonal adherence to influenza vaccine uptake in the group of the population with a chronic condition for which seasonal influenza vaccination is recommended (43), this information could be important to increase vaccine coverage in this target group. Second, we used an alternative method to estimate influenza severe burden in Portugal to better fit the impact study. Given the ecologic nature of the adopted approach, it was important to have specific outcomes and also that had correspondence to the outcome of IVE estimates.



Previous research in Portugal provided estimates of influenza excess associated hospitalizations (3) and all-cause deaths (2) that were based on time series approaches. Although these methods are more comprehensive approaches and often used to measure influenza burden (44), in our case, it was important to use specific influenza-related outcomes for impact estimation. We used hospitalized SARI and intra-hospital deaths, restricted to epidemic periods, to improve specificity. Also, it was important to have an outcome that was highly correlated with IVE estimates. Finally, to increase external validity we used i) a national discharge database, ii) an influenza laboratory diagnoses database that collects influenza positivity results from hospitals distributed at national level; iii) influenza vaccine effectiveness from meta-analysis and iv) vaccine coverage estimates from a population-based survey. Moreover, to reduce potential heterogeneity related to different codification procedures, the study was restricted to only 3 seasons, but that with different pattern of the influenza virus circulation. All these using registry/ monitoring data easily accessible that can be replicable each season. Following the example of the USA (45), these results, along with the burden and effectiveness results can be reported, so to better communicate the influenza vaccination benefits.

## Conclusion

The influenza vaccination strategy in place in Portugal for the 65 and more years individuals and individuals with chronic conditions, prevented on average 1833 hospitalizations and 383 deaths per season. The applied method identified and quantified the overall benefits of the influenza vaccination program, even in seasons with limited vaccine effectiveness. Also, it captured the impact of several outcomes with different levels of severity.

Given the already mentioned, multiple data source ecological nature of the study; further investigations are warranted, with the perspective of evaluating the sensibility of the approach in other seasons, countries and data sources.

The knowledge on health benefits in terms of influenza-related hospitalizations and deaths averted by the vaccination program will allow better understanding the impact of the national vaccination strategies and strengthening public health communication with the general public and policymakers, to support public health plans towards the increase of vaccine coverage in high-risk groups.

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Table 2. List of diagnosis codes for which patients could be screened for onset of SARI symptom, IMOVE+ hospital based IVE studies

Category	Morbidity	ICD-9	ICD-10
Influenza like illness	Cough	786.2	R05
	Difficulty breathing	786.05	R06
	Sore throat	784.1	R07.0
	Dysphagia	787.20	R13
	Fever	780.6	R50.9
	Headache	784.0	R51
	Myalgia	729.1	M79.1
	Fatigue/malaise	780.79	R53.1, R53.81,

			R53.83
Cardiovascular diagnosis	Acute myocardial infarction or acute coronary syndrome	410-411, 413-414	I20-23, I24-25
	Heart failure	428 to 429.0	I50, I51
Respiratory diagnosis	Emphysema	492	J43.9
	Chronic obstructive pulmonary disease	496	J44.9
	Asthma	493	J45
	Myalgia	729.1	M79.1
	Dyspnoea/respiratory abnormality	786.0	R06.0
	Respiratory abnormality	786.00	R06.9
	Shortness of breath	786.05	R06.02
	Other respiratory abnormalities	786.09	R06.00, R06.09, R06.3, R06.89
Infections	Pneumonia and influenza	480-488.1	J09-J18
	Other acute lower respiratory infections	466, 519.8	J20-J22
	Viral infection, unspecified	790.8	B34.9
	Bacterial infection, unspecified	041.9	A49.9
	Bronchitis	490, 491	J40, 41
Inflammation	SIRS non infectious without acute organ dysfunction	995.93	R65.10
	SIRS non infectious with acute organ dysfunction	995.94	R65.11
Diagnoses related to deterioration of general condition or functional status	General physical deterioration, lethargy, tiredness	780.79	R53.1, R53.81, R53.83
	Anorexia	783.0	R63.0
	Feeding difficulties	783.3	R63.3
	Abnormal weight loss	783.21	R63.4
	Other symptoms and signs concerning food and fluid intake	783.9	R63.8
	Desorientation/Altered mental status	780.97	R41.0
	Dizziness and giddiness	780.4	R42
	Infective delirium	293.0, 293.1	F05
	Coma	780.01	R40.2
	Transient alteration of awareness	780.02	R40.4
	Other alteration of consciousness (Somnolence, stupor)	780.09	R40.0, R40.1
	Febrile convulsions (simple), unspecified	780.31	R56.00
	Complex febrile convulsions	780.32	R56.01

*\*SIRS: Systemic inflammatory response syndrome*

#### **Declarations**

#### **Abbreviations**

CI – Confidence Interval

EU – European Union

ICD – International Classification of Diseases

IRE – Influenza-Related events

IVE – Influenza Vaccine Effectiveness

NAE – Number of Averted Events

NNV – Number Needed to Vaccinate

PF – Prevented Fraction

SARI – Severe Acute Respiratory Illness

VC- Vaccine Coverage

#### ***Ethics approval and consent to participate***

This study corresponds to a secondary data analysis of the Hospital Discharge dataset, which is collected by the Health Systems Central Administration (Administração Central do Sistema de Saúde, ACSS). The ACSS provides anonymized data for epidemiological research. The anonymization implies the removal of any personal data. According to the National Ethics Committee for Clinical Research “Personal data that has been rendered anonymous in such a way that the person is not or no longer identifiable is no longer considered personal data and is therefore not covered by article 3 of the General Data Protection Regulation” (<https://www.ceic.pt/documents/20727/57550/RGPD/d48e1ec0-39bd-437e-96ca-ffd740c8b732> - page 2). For this reason the study protocol was not submitted to an ethical committee.

#### **Consent for publication**

Not applicable

#### **Availability of data and materials**

The Hospital Discharge dataset is not publicly available. The Health Systems Central Administration (Administração Central do Sistema de Saúde, ACSS) provides the Hospital Discharge dataset to the National Health Institute in a regular basis. This dataset is anonymized and may be used for epidemiological studies. The aggregated data used in this specific study is available from the corresponding author upon reasonable request.

#### **Competing interests**

The authors declare that they have no competing interests.

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#### **Authors' contributions**

AM designed, planned the study, interpreted results and wrote the original draft of the manuscript. IK extracted and analysed all the data and was a major contributor in writing the manuscript. AL, CMD and BN collaborated in conceptualization of the study and the interpretation of results and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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## 6 Discussion

The overall purpose of developing this thesis was to contribute to the national influenza vaccination strategy, by providing epidemiological information on three key components: influenza vaccine coverage, influenza vaccine effectiveness and impact of the influenza vaccination strategy. With focus in a sub-group of the population that is targeted for yearly influenza vaccination, i.e., older adults with 65 or more years and individuals with a chronic condition with indication for the influenza vaccine. Our main intent was to quantify vaccine coverage and identify associated factors and as well as quantifying the vaccine effectiveness and the reduction of influenza risk and its complications by the yearly vaccination.

This thesis section is dedicated to the overall discussion of the thesis results and limitations/strengths, as well some consideration on potential implications for public health practice and research.

### 6.1 Main findings

#### 6.1.1 Influenza vaccine coverage and associated factors

One of the first pillar of any immunization program is the knowledge on how many persons are vaccinated. It allows to capture the success of the program implementation and identify potential sub-groups with low vaccine uptake (248). The influenza and influenza vaccine specificities implies a yearly vaccination and thus, monitoring of the influenza vaccine coverage needs to be done also every season.

##### *What was known*

In Portugal, the influenza vaccine coverage is measured on a yearly basis since 1998 (19,100). However, the proportion of high-risk individuals that take the influenza vaccine on a regular basis, i.e., every year, was unknown. Also, the influenza vaccine monitoring system revealed that for both older adults with 65 and more years and individuals with chronic conditions, the influenza vaccine coverage target of 75% was still far from being achieved. As such, finding the factors that may promote IV uptake was extremely important so to increase the vaccine coverage in a season and consecutive seasons. Although some work was done in the associated factor for IV uptake in a given season for Portugal (121), these results needed to be updated and there was still missing research on the factors that were associated to yearly and regular influenza vaccine uptake.

##### *What this study adds*



Results obtained in study 2 support that the proportion of high-risk population that take the vaccine on a yearly basis was considerable low, of approximately 27%. To analyze the main factors associated to IV uptake, a conceptual model was designed (study 1). The conceptual model was based in the premises that vaccine uptake is a personal behavior in its essence but needs to be contextualized to be further understood. In summary, to better predict and act towards the increase of the IV uptake, there is a need to understand the contribution of different dimensions (either personal, family, cultural, community and country context) and their effect. As such, the social ecologic model first adapted to pandemic vaccine by Kumar et al. (125) was also adapted, for the first time to my knowledge, to the seasonal influenza vaccine in the Portuguese context.

According to the approach, there are 5 levels or layers (1) individual or (intra)personal, 2) interpersonal, 3) organizational, 4) community and 5) policy) that can influence IV uptake. For pandemic vaccine, Kumar et al. (125) found that all the 5 levels were associated to both pandemic vaccine uptake and intention to the vaccinated in following years (125). In study 1, however, the results pointed to a different direction: for both men and women main contributor to IV uptake were individuals and organizational level. For women, the community level was also relevant in the IV uptake.

Study 1 and study 2 intended to fulfill the lack of knowledge on main factors associated to IV uptake, either on a given season (study 1) or repeated seasons (study 2). Looking at specific factors, the study's results enhances, the importance of a health professional on the adoption and maintenance of this preventive measure. Overall, younger age, women, smokers and individuals with a cardiovascular diseases should be targeted in tailored influenza vaccination programs.

### 6.1.2 Influenza vaccine effectiveness

Concomitantly to vaccine coverage, the influenza vaccine effectiveness is a major component of the vaccination program. High vaccine effectiveness is a key requirement to achieve high vaccine direct and indirect effect.

#### *What was known*

At national level, since 2008 an yearly effort has been in place to obtain early in the season and end of season influenza vaccine effectiveness estimates. By implementing the test-negative EuroEVA/I-MOVE study at primary care, it was possible to identify seasons with sub-optimal vaccine protection in preventing medically attended influenza (137,249). EuroEVA data contributed also to the European multicentric study (I-MOVE)

and for obtaining pooled European IVE estimates. The European compiled work of several seasons, allowed to understand further the vaccine waning effect (136) and the effect of repeated vaccination (181). Nevertheless, there were still several influenza vaccine effectiveness related factors that needed to be further investigated.

Also, the effectiveness of the vaccine against medically attended influenza only captures one aspect of the potential benefit of the influenza vaccine. At national level, was still unknown the vaccine added protection against more severe outcomes, as hospitalizations. Moreover, and given the need for multicentric studies to obtain IVE estimates with good precision, there was the need to evaluate the national data quality and study validity that was further incorporated in the European pooled estimates.

#### *What this study adds*

One aspect of the IVE related factors that needed to be investigated was the potential influenza vaccine effect modifier by age and chronic conditions. Study 3 was based on ten seasons of EuroEVA data and intended to add some knowledge on this subject. Due to sample size, results were however inconclusive. Point estimates were against the hypothesis of lower IVE in the chronic condition strata and different results were obtained when looking to the age modifier effect on IVE against different (sub)types. Main conclusion is the need for further studies with higher sample size.

Study 4 reports the result of implementing EVA Hospital, the Portuguese study to measure IVE against hospitalizations in the older adults with 65 and more years. By implementing EVA Hospital, it was possible to pilot the test-negative design in a hospital context for the first time in Portugal and to start the creation of a national network. Data collected during three season contributed also to the European IVE hospital network, allowing the seasonal estimation of IVE (141,250) and enough sample size to study the effect of repeated vaccination on IVE against hospitalizations (147).

### 6.1.3 Impact of the influenza vaccination program

The national influenza vaccination strategy is the main public health intervention to mitigate influenza infection and related complications. As such, it has an overall effect at population level that is not reflected by the usually reported vaccine effectiveness measures, and has been considered by some authors as a way of measuring the impact of the vaccination program (15,17).

#### *What was known*

Although considered as of extreme importance, particularly to demonstrate the benefits of the yearly vaccination (17), measuring the impact of the influenza vaccination program is challenging. Either because of the difficulties in estimating influenza burden (10,251); of having adequate IVE estimates (213) or unbiased population specific vaccine coverage (3,252).

In the USA, the CDC has been measuring the impact of the vaccination program on a yearly basis by estimating the number of averted influenza cases, medically attended influenza cases and hospitalizations (253). The approach that has been used includes the estimation of prevented influenza cases in the population (using data on vaccine coverage and effectiveness) and the number of observed influenza related outcomes. In Europe, although some country specific estimates were reported on averted mortality (33), there were no reports at European level that could complement the annual IVE estimates.

#### *What this study adds*

Study 5 intended to address this issue, by developing and implementing a common protocol in Portugal, Spain and the Netherlands. The results indicate that it was feasible to harmonize both outcome definitions and IVE estimates along the countries to produce comparable annual estimates of the number of averted medically attended influenza at primary care.

Moreover, it established a methodological approach that could be used in other influenza outcomes, such as hospitalizations and deaths. This was accomplished in study 6. Using the methodological approach defined in study 5, the impact of the vaccination program was measured in terms of hospitalizations and deaths. Overall, the impact study's results (study 5 and 6) indicate benefits from vaccination. This is the first time that the impact of the national influenza vaccination program was measured, by quantifying the number of averted influenza outcomes. It covered different influenza severity outcomes and main conclusions is that even in seasons with low IVE, there are positive effects of vaccination.

## 6.2 Strengths and limitations

Albeit the thesis achievements, there are inherent limitations to be acknowledge. All the studies developed within the ambit of the thesis are of observational nature, and specific studies limitations and strengths were previously discussed in the result section. This section is dedicated to overall thesis limitations and strengths.

Starting with the population under study. The thesis focused on community dwelling older adults with 65 and more years and individuals with chronic. However, high-risk population with potential post-infection complications goes beyond the previous. It includes children with less than 5 years, institutionalized individuals and pregnant women (9).

At national level, the influenza vaccination program targets older adults, individuals with chronic conditions and pregnant woman's (13) and does not include children with less than 5 years with no associated morbidities. As such, the work conducted focused in two out of the three sub-groups of the high-risk population. Estimates from Statistics Portugal indicate that in 2014-2017, there were on average 2 176 912 older adults with 65 and more years; 1 750 671 individuals with less than 65 years with a chronic condition and 85 286 pregnant (246). This thesis thus covered approximately 98% of the high-risk population that was targeted for annual influenza vaccination.

All through the thesis, an effort was done to use national databases. It was the case for study 1 and 2, which used data from the National Health Survey (study 1) and from the National Health Survey with Physical Examination (study 2). These two databases included both Portugal mainland and autonomous regions, and are representative of the Portuguese population. In addition, the NHS is an official statistics survey that is intended to be implemented every 5 years, and thus allows the continued monitoring of IV uptake determinants. In study 3, the EuroEVA study has a national coverage; recruited general practitioner are distributed in Portugal Mainland and Islands (130,254). Finally, in study 5, the impact on medically attended influenza, was conducted using data from the national influenza surveillance system, that covers the country (231).

However, this national coverage was not succeed in study 4. At national level, only two hospitals, both located in the same region of Lisbon participated by collecting SARI cases. Although study results indicate the presence of internal validity, which allowed contributing to obtain European estimates, the final sample size was not sufficient to ensure good precision estimates at national level. Finally, the study on the impact of the vaccination program on hospitalizations and deaths (study 6), was based on data from the hospital discharge database. Although covering all hospitalizations that occurred in mainland Portugal, this database does not include hospitalizations that occur in private hospitals or in the autonomous regions and may represent 20% of the hospitalizations (245). Moreover, in its current state, final databases are only available for research with 2 years delay. As such, data on hospitalization and intra-hospital

deaths may compromise the timeliness of obtaining, on yearly basis, the impact of the vaccination in more severe outcomes.

There are also some methodological limitations to be referred in the thesis. In the vaccine coverage and associated factors studies, I used cross-sectional studies. Although appropriate to estimate population based proportions, as the vaccine coverage, this study design is less suitable to estimate causal effects. This limits the interpretation of the results and inhibits the possibility to find IV uptake predictors. Given this limitation, through out the thesis, these variables were designated as associated factors.

Another methodological limitation is the approach used to estimate the impact of the vaccination program. Impact was defined as the overall effect (that results from both direct and indirect effect of the vaccination), assuming the vaccination program as exposure (15). The estimation method used in the thesis only allows quantifying the direct effect, by using the vaccine coverage and vaccine effectiveness. Indirect effect was considered null. Given the low vaccine coverage in majority of the population sub-groups (100), the indirect effect on medically attended influenza or hospitalizations was supposed to be residual.

However, previous systematic review and meta-analysis, estimated that some indirect effect on older adults mortality could be observed (255). Eichner et al (204) simulations, estimated that even with the quadrivalent vaccine coverage in children as low as 20%, indirect effect could exceed the direct ones by a factor of 20 to 30. Considering that in Portugal the vaccine coverage in population aged 0-15 years was below 5% and with less than 64 years ranged between 7% and 18% (20), the impact of the vaccination program could be underestimated, particularly in more severe outcomes.

Additionally, in seasons with high vaccine effectiveness and coverage, with consequent reduced or null observed influenza burden, the number of averted events derived by the NAE equation would be low or zero. This contradiction was pointed out by Foppa et al. (213), referring that in extreme, even in an ideal scenario where the vaccine disrupt influenza transmission and all events are averted, the impact would be null as no burden would be identified and measured. As such, the adopted approach only works when there is observed burden of influenza.

To achieve internal validity, the impact study depends on the outcome's sensitivity/specificity and its correspondence with the IVE estimates outcome. In both impact studies (study 5 and 6), the selection of the data sources and IVE estimates

were done keeping the premises i) reflects influenza burden and ii) correspondence to outcome of IVE estimates. This was an added step considering previous impact studies (32,33,213).

On the down side, external validity depends not only on the outcome definition but also on the representativeness of the target population of the data sources used for measuring them. The administrative registries, such as the hospital administrative databases and vaccine coverage survey that were used, were limited to mainland Portugal. Moreover, they do not reflect the same population as vaccine coverage is collected only in community dwelling population and hospital database include also institutionalized. Census data from national statistics indicate that in 2011 there were 84894 institutionalized individuals (73 230 of which in residential or nursing home) aged 65 and more years. This corresponds to a proportion of approximately 4% of the older adult population that is represented in the hospital database but not on the vaccine coverage survey. This low proportion of institutionalized older adult population in Portugal, support that the potential overestimation of the hospitalization burden (and respective vaccination impact) on community dwelling older adult was also low.

## 6.3 Implications for public health practice and research

This thesis focused in three components of the national influenza vaccination program. Despite the limitation already acknowledged, the results obtained within the thesis can be useful to improve the national influenza vaccination program.

The first improvement would be on the vaccine coverage. In order to increase and sustain the proportion of high-risk individuals that take the influenza vaccine, it is important to focus on the individuals less prone to take the vaccine on a given year and maintain the regular uptake. As results indicate that among high-risk population, younger individuals, female and smoker were less likely of being vaccinated on a season and of regular vaccine uptake, tailored vaccination strategies could be developed to overcome vaccine hesitancy (256). The interaction with healthcare system and recommendation from health professional are well established contextual barriers for vaccine hesitancy (108), and were also found significantly associated to IV uptake in Portugal. This constitutes an important setting for IV uptake recommendation and administration, and could be important to reduce missed opportunities, especially for younger individuals (257).

Traditional strategies for improving vaccination include among others, reminder or recall system, clinician decision support based on electronic health record and free access to vaccine (257,258). However, these strategies should be adapted to each

sub-group specific barriers towards the vaccine. Given the specific physical and contextual barriers that are inherent to each region, it would be important to develop more research on this topic.

Also lacking research are the predictors of the first IV uptake. For instance, even though previous influenza infection has been identified as important IV uptake (108), it is not clear if this could be an important predictor in Portugal and if it would be important in all sub-groups of the population.

Monitoring of IVE early in the season on a yearly basis is an imperative for early action in seasons with lower than expected vaccine protection. Additionally, research on IVE effect modifier is relevant for the IV program strategy. Further research, with higher sample sizes, could elucidate whether or not other sub-groups of the population could be targeted (259).

Other research questions on IVE studies still need to be addressed or enlighten. Namely, the role of previous infections and immunity, of the virus genetic changes on vaccine failures. For that, large databases with good quality data are needed. This reinforces the need for maintaining and strengthening the national (EuroEVA and EVA Hospital) and European networks.

One important factor in reducing vaccine hesitancy is the knowledge on both the influenza and its vaccine. Improving communication in both the population and to decisions makers could be relevant in reducing this barrier. The results of the current thesis could be important in informing both sub-groups. Quantifying the influenza event prevented from the current program and its distribution on the population, could contribute to more informed decisions. From the public health perspective, the knowledge of vaccine-prevented fraction for each influenza-associated outcome could be a better indicator of the vaccine benefits. This information could be of great importance in particular in the subgroup of individuals more at risk of complications due to influenza. This was the rationale for CDC to integrate and provide on a yearly basis the burden of influenza and what was averted by the vaccination program (31).

The impact estimates could play a key role in influenza vaccination policies in Portugal. Changing a national vaccination strategy involves evaluating the existing one and compare the potential gain with a new plan. Therefore, to provide decision makers with timely information to support their decisions on influenza vaccine it is important to evaluate the strategy impact.

The impact estimation, although simple and fast, does not include the indirect effect. It is important to continue conducting research so to overcome this issue. In addition, the

estimation of the influenza burden still needs to be improved. Main approaches used in this thesis were indirect, and this could provide biased estimates. It is thus important to improve influenza surveillance, particularly in more severe outcomes so to reduce burden overestimates. Namely, by including other respiratory virus information and other potential confounders (76). Moreover, it would be important to estimate influenza burden looking to other outcomes, namely, use of intensive care units and influenza mortality. This global view on influenza burden and respective vaccination impact may provide a more realistic estimate of the annual influenza vaccine strategy.





## 7 Conclusions

In Portugal, a risk-based influenza vaccine strategy has been in place, where annual recommendation include vaccinating the older adults aged 65 and more years and >6 months individuals with chronic conditions (high-risk groups). As any other public health program, it is important to evaluate the implementation and impact on the population that is targeted in the program. As such, an annual effort needs to be in place to translate to health professionals, general population and to decision makers the coverage, the direct and overall effect of the vaccination strategy implemented that year.

All the studies developed within this thesis aimed to contribute to the evaluation of the national influenza vaccination program. It provided information on population estimates of influenza vaccine coverage and associated factors, on one and repeated seasons, and quantified the reduction of influenza and its complications due to vaccination. Overall results, indicate that regular annual influenza vaccine uptake is suboptimal in high-risk individuals and that the vaccine effectiveness, although with no evidence of effect modification by age or chronic condition, was low or moderate in preventing medically attended influenza in primary care or hospitalization. However, besides these lower than expected vaccine coverage or effectiveness, the vaccination program had positive and consistent impact at population level. The impact studies revealed relevant reduction on all studied influenza outcomes due to the vaccination program, even in seasons with low vaccine effectiveness.

The overall impact of the influenza vaccination program may however be improved by changing three important parameters: i) vaccine coverage; ii) vaccine effectiveness; iii) influenza burden.

In relation to the increase of vaccine coverage, this study contributed by developing a framework and methodological approach that can be used to continue monitoring the factors that are associated to vaccine uptake. Ultimately, this allows the identification of individuals with vaccine hesitancy and find main vaccine uptake barriers that could be used as opportunity for improving the vaccination strategy.

Concerning vaccine effectiveness, the way to improve the direct effect of the vaccine may only be achieved by higher performance vaccines. Either through changing the trivalent inactivated vaccines into existing adjuvant or high dose vaccines, or through research for new and improved vaccines. Although this thesis did not focused directly this field, it did contributed for the annual monitoring of the vaccine effectiveness and explored the potential age and chronic condition effect modifier, that could have

consequences on the actual high-risk vaccination strategy. It allowed the implementation of a national IVE study within a hospital setting. Alongside with the primary care based studies, these IVE studies permit the yearly monitoring of the protection conferred by the influenza vaccine. Furthermore, it constitutes the necessary database and framework for solid and robust research on vaccine effectiveness.

Ultimately, reducing influenza burden depends on the population health status, as higher influenza impact is observed in the more frail population. This overall improvement on health status can result from integrated public health strategies to reduce morbidity, and this is the target of all national Priority Health Programs. Although this study did not focus directly on this subject, it contributed to the reflection on measuring influenza burden in all high-risk individuals, namely on adults with chronic condition.

Finally, a methodology was developed and implemented allowing the annual evaluation of the impact of the influenza vaccine strategy. It allows to capture the impact of the IV strategy in multiple outcomes such as averted consultations, hospitalizations and even deaths. This methodology has the potential for full implementation in the future, continuous evaluation of the existing one or to evaluate changes in the strategy. Continuous research efforts need to be in place so enhance the national program towards the maximum public health impact.

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# Annex

## 8.1 Questionnaires

Nome: \_\_\_\_\_

N.º Cartão de utente/ Proc. Clínico: \_\_\_\_\_

Código de casa \_\_\_\_\_ - \_\_\_\_\_

(Deixar em branco)

<b>REPUBLICA PORTUGUESA</b> <small>GOVERNO DA REPÚBLICA</small>		<b>Effectividade da Vacina Antigripal EuroEVA - 2017/2018</b>																																									
<b>Código do Médico</b> _____ <b>Unidade de saúde / Médico</b> _____		<b>Código de casa</b> _____ - _____																																									
<b>Código do Médico</b> _____ <b>Unidade de saúde / Médico</b> _____		<b>A preencher pelo INSA</b> Nº EVA _____ Raq _____ Data ____/____/_____ Amostra: DNF <input type="checkbox"/> Ouro <input type="checkbox"/> Técnico <input type="checkbox"/>																																									
<b>O doente não pertence à minha lista</b> <input type="checkbox"/> <b>Data de Colheita</b> ____/____/_____ <small>(dd / mm / aaaa)</small>		<b>Pesquisa de vírus</b> Negativo <input type="checkbox"/> { AH1pdm09 <input type="checkbox"/> AH3 <input type="checkbox"/> Positivo <input type="checkbox"/> { B/Vic <input type="checkbox"/> B/Yam <input type="checkbox"/> B <input type="checkbox"/>																																									
<b>Informação Relativa ao Doente</b> Sexo <input type="checkbox"/> Masculino <input type="checkbox"/> Feminino		<b>Data de nascimento</b> ____/____/_____ <small>(dd / mm / aaaa)</small>																																									
<b>Síndrome Gripal</b> <b>Data de início dos sintomas</b> ____/____/_____ <small>(dd / mm / aaaa)</small> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td>Início súbito (&lt;24h)</td> <td>S</td> <td>N</td> <td>D</td> </tr> <tr> <td>Febre ou febrícula _____ °C</td> <td>S</td> <td>N</td> <td>D</td> </tr> <tr> <td>Mai-estar geral, debilidade, prostração</td> <td>S</td> <td>N</td> <td>D</td> </tr> <tr> <td>Cefaleia</td> <td>S</td> <td>N</td> <td>D</td> </tr> <tr> <td>Mal-estar geral, dores generalizadas</td> <td>S</td> <td>N</td> <td>D</td> </tr> <tr> <td>Tosse</td> <td>S</td> <td>N</td> <td>D</td> </tr> <tr> <td>Dor de garganta, inflamação da mucosa nasal e faríngea, sem sinais respiratórios relevantes</td> <td>S</td> <td>N</td> <td>D</td> </tr> <tr> <td>Dificuldade respiratória</td> <td>S</td> <td>N</td> <td>D</td> </tr> <tr> <td>Calafrios/arrepios</td> <td>S</td> <td>N</td> <td>D</td> </tr> <tr> <td>Contacto com doente com gripe</td> <td>S</td> <td>N</td> <td>D</td> </tr> </table>		Início súbito (<24h)	S	N	D	Febre ou febrícula _____ °C	S	N	D	Mai-estar geral, debilidade, prostração	S	N	D	Cefaleia	S	N	D	Mal-estar geral, dores generalizadas	S	N	D	Tosse	S	N	D	Dor de garganta, inflamação da mucosa nasal e faríngea, sem sinais respiratórios relevantes	S	N	D	Dificuldade respiratória	S	N	D	Calafrios/arrepios	S	N	D	Contacto com doente com gripe	S	N	D	<b>Tomeu antiérbico durante os últimos 14 dias?</b> <input type="checkbox"/> Não <input type="checkbox"/> Sim, o doente <input type="checkbox"/> Sim, um co-habitante <b>Nome do antiérbico</b> <input type="checkbox"/> Oseltamivir (Tamiflu) <input type="checkbox"/> Zanamivir (Relenza) <input type="checkbox"/> Outro <b>Vai ser tratado com antiérbico</b> <input type="checkbox"/> S <input type="checkbox"/> N <b>Nome do antiérbico</b> _____ <b>Colar na sangria</b>	
Início súbito (<24h)	S	N	D																																								
Febre ou febrícula _____ °C	S	N	D																																								
Mai-estar geral, debilidade, prostração	S	N	D																																								
Cefaleia	S	N	D																																								
Mal-estar geral, dores generalizadas	S	N	D																																								
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Dor de garganta, inflamação da mucosa nasal e faríngea, sem sinais respiratórios relevantes	S	N	D																																								
Dificuldade respiratória	S	N	D																																								
Calafrios/arrepios	S	N	D																																								
Contacto com doente com gripe	S	N	D																																								

Legenda: S – sim N – não D – desconheço

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Questionário Síndrome Gripal (continuar as respostas diretamente com o(a) doente)

Código da casa: _____ - _____				
Nesta época (2017/2018), o(a) doente foi vacinado(s) contra a gripe?	S	N	D	
Se sim, vacinado em (se não sabe a data exata, indique a mais aproximada)	____ / ____ / ____			
Qual era o nome da vacina? _____ Não sabe <input type="checkbox"/>	(dd / mm / aaaa)			
O doente foi vacinado contra a gripe sazonal na época 2016/2017?	S	N	D	
O doente foi vacinado contra a gripe sazonal na época 2015/2016?	S	N	D	
O doente é profissional de saúde ou cuidador num lar/casa de idosos?	S	N	D	
O(a) doente é co-habitante ou cuidador de crianças que tenham risco elevado de desenvolver complicações, cuja idade é < 6 meses?	S	N	D	
A doente encontra-se grávida?	S	N	D	NA
Se sim em que trimestre se encontra?	____ Não sabe <input type="checkbox"/>			
História tabágica do(a) doente: F (Fumador) ExF (Ex-fumador) NEF (Nunca fumou) D (Desconhecido)	F	ExF	NEF	D
O doente toma estatina?	S	N	D	Desde quando toma estatina? ____ / ____
Diabetes	S	N	D	
Doença cardiovascular (cardiopatia congénita, hipertensão, insuficiência e insuficiência cardíaca crónica)	S	N	D	
Doença renal crónica (insuficiência renal crónica, síndrome nefrótica)	S	N	D	
Doença hepática crónica (cirrose, doença biliar, hepatite crónica)	S	N	D	
Obesidade (IMC >30)	S	N	D	
Doença respiratória crónica (asma, bronquite crónica, enfisema, fibrose quística, pneumonia crónica, doença broncopulmonar, fibrose pulmonar)	S	N	D	
Imunodeficiência congénita ou adquirida	S	N	D	
Doença neuromuscular com comprometimento da função respiratória	S	N	D	
Número de hospitalizações devido a uma destas doenças crónicas nos últimos 12 meses	____ Não sabe <input type="checkbox"/>			
Número de consultas de medicina geral e familiar, nos últimos 12 meses	____ Não sabe <input type="checkbox"/>			
Quantos anos de escolaridade o doente completou com aproveitamento?	____ Não sabe <input type="checkbox"/>			
Quantas pessoas vivem na mesma casa com o(a) doente? (familiares ou não familiares, sem contar com o doente)	____ Não sabe <input type="checkbox"/>			
O(a) doente necessita de ajuda para tomar banho? (aproximadamente viver há no mais anos de idade)	S	N	D	NA

Legenda: S - Sim; N - Não; D - Desconhecido; NA - Não aplicável



Código de caso

C H L C - [ ] [ ] [ ]

(Estado da Prefeitura da cidade Antigo) em Coimbra Hospital

<p><b>Nome da criança:</b></p> <p>_____</p> <p><b>Idade:</b></p> <p>_____</p> <p><b>Sexo:</b></p> <p>_____</p> <p><b>Data de nascimento:</b></p> <p>____/____/____</p> <p><b>Data de início dos sintomas:</b></p> <p>____/____/____</p>		<p><b>Informação sobre os Participantes</b></p> <p>Sexo <input type="checkbox"/> Masculino <input type="checkbox"/> Feminino</p> <p><b>Data de nascimento:</b></p> <p>____/____/____</p> <p><b>Critérios de inclusão</b></p> <p>Gripe prévia <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Exercício institucionalizado <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Contato com a gripe <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Exercício em alta hospitalar mesmo no início dos sintomas <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p>	
<p><b>Estado de sintomas</b></p> <p>Início súbito (SI) <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Febre ou febre <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Mal-estar geral, dor de cabeça, dor no corpo <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Catarrho <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Mal-estar, dor no corpo <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Tosse <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Coriza <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Dificuldade respiratória <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Degeneração do estado geral <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p>		<p><b>Resultados laboratoriais</b></p> <p><b>Data de coleta:</b></p> <p>____/____/____</p> <p><b>Presença de vírus</b> <input type="checkbox"/> Negativo <input type="checkbox"/> Positivo</p> <p><b>Tipos de vírus</b> A <input type="checkbox"/> B <input type="checkbox"/></p> <p><b>Subtipos de vírus</b> A/H1N1 <input type="checkbox"/> A/H3N2 <input type="checkbox"/></p> <p><b>Outros</b></p> <p>Varicela <input type="checkbox"/> Sarampo <input type="checkbox"/> Dengue <input type="checkbox"/></p>	
<p><b>Antecedentes e sintomas</b></p> <p>Tomeu antibiótico nos 14 dias que antecederam a coleta? <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p><b>Nome do antibiótico (AC)</b> _____</p>		<p><b>Tomeu antibiótico nos 14 dias que antecederam a coleta?</b> <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p><b>Nome do antibiótico (AC)</b> _____</p>	
<p><b>Vacina antigripal</b></p> <p>Recebeu vacina (2016/2017) ou (vacina) foi vacinado(a) contra a gripe? <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p><b>Vacinado em:</b> ____/____/____</p> <p><b>Nome da vacina:</b> _____</p> <p>O doente foi vacinado contra a gripe antes da época 2016/2017? <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p>		<p><b>Vacina anti-pneumocócica</b></p> <p>O(a) doente foi vacinado(a) com a vacina anti-pneumocócica PPV23? <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p><b>Vacinado em:</b> ____/____/____</p> <p>O(a) doente foi vacinado(a) com a vacina anti-pneumocócica PCV13? <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p><b>Vacinado em:</b> ____/____/____</p>	

Comorbilidades e outros fatores							
Doença renal crônica	S	N	D	Doença	S	N	D
Doença pulmonar crônica	S	N	D	Antecedentes de AVC	S	N	D
Pressão alta (nos últimos 6 meses)	S	N	D	Diabetes	S	N	D
Doença reumatológica crônica	S	N	D	Asma	S	N	D
Câncer hematológico	S	N	D	Cardiopatia	S	N	D
Doença oncológica não hematológica	S	N	D	Obesidade (IMC ≥ 30)	S	N	D
Insuficiência renal aguda ou crônica	S	N	D	Défice nutricional	S	N	D
Doença Hepática Crônica	S	N	D				

Nos últimos 12 meses, quantas vezes foi o(a) doente hospitalizado devido a uma das doenças crônicas?

Número de consultas no hospital nos últimos 6 meses?

Número de consultas de Medicina Geral e Familiar nos últimos 6 meses?

Problema(s) do(a) doente    F    ExF    NF    D

**Dependência**

O(a) doente apresenta-se dificuldade a realizar alguma destas atividades, antes do internamento? (pode assinalar mais do que uma opção)

Alimentar-se ☐

Atender as suas necessidades básicas ☐

Fazer a sua higiene pessoal ☐

Caminhar/locomover-se sozinho ☐

Tomar banho ☐

Cambiar roupa/sapato/roupado ☐

Subir/descer escadas ☐

Admissão na UCI    S    N    D    Data    \_\_\_\_/\_\_\_\_/\_\_\_\_    2    3    4    5    6    7    8    9    10    11    12    13    14    15    16    17    18    19    20    21    22    23    24    25    26    27    28    29    30    31    32    33    34    35    36    37    38    39    40    41    42    43    44    45    46    47    48    49    50    51    52    53    54    55    56    57    58    59    60    61    62    63    64    65    66    67    68    69    70    71    72    73    74    75    76    77    78    79    80    81    82    83    84    85    86    87    88    89    90    91    92    93    94    95    96    97    98    99    100    101    102    103    104    105    106    107    108    109    110    111    112    113    114    115    116    117    118    119    120    121    122    123    124    125    126    127    128    129    130    131    132    133    134    135    136    137    138    139    140    141    142    143    144    145    146    147    148    149    150    151    152    153    154    155    156    157    158    159    160    161    162    163    164    165    166    167    168    169    170    171    172    173    174    175    176    177    178    179    180    181    182    183    184    185    186    187    188    189    190    191    192    193    194    195    196    197    198    199    200

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## 8.2 Ethical and Data Protection clearance

Comissão de Ética

Nota Interna N.º 2 /2012

De: Secretariado da Comissão de Ética

Data: 18 Janeiro 2012

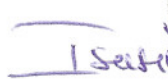
Para: Baltazar Nunes

Assunto: Pedido de apreciação e parecer – projecto " Euroeva "

No seguimento do seu pedido de apreciação e parecer, relativo ao projecto de investigação *EUROEVA – Efectividade da Vacina Antigripal na Europa*, vimos por este meio informar que o mesmo mereceu parecer positivo da Comissão de Ética deste Instituto, nos termos da autorização dada pela Comissão Nacional de Protecção de Dados. Aproveitamos, ainda, para desejar o maior sucesso no desenvolvimento deste trabalho.

Com os melhores cumprimentos,

O Secretariado da Comissão de Ética

 **Comissão de Ética**  
**INSA, I.P.**

APRECIACÃO DO ESTUDO CLÍNICO

Nome do Projecto: EM-Hospitalar - estudo da efectividade do  
Vacini antigripal contra febre e gripe de (nd - IMORE)

Refª ..... Especialidade: ..... Do CHLC ☐

Investigador: ..... Externo ☐

Decisão do Conselho de Administração ☐ Director Clínico ☒

Aprovado ☒ Não Aprovado ☐

Pedidos elementos adicionais ☐

Obs.:

Parecer da Comissão de Ética

Favorável ☒ Não Favorável ☐

Pedidos elementos adicionais ☐

Recomendações:

Obs.:

Parecer do Centro de Investigação

Favorável ☐ Não Avaliado ☒ Não Favorável ☐

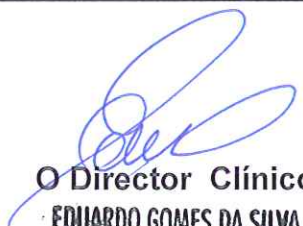
Pedidos elementos adicionais ☐

Recomendações:

Obs.:

Data 9 / 10 / 15

O Conselho de Administração

  
O Director Clínico  
EDUARDO GOMES DA SILVA  
Director Clínico



## COMISSÃO DE ÉTICA PARA A SAÚDE

### Parecer

Data: 01.10.2015

Processo n.º 239/2015

**Assunto:** "EVAHospital – Estudo da Efectividade da Vacina Antigripal contra Formas Graves de Gripe (da rede I-MOVE)"

**Relator:** Dra. Cristina Lima

**Promotor:** O Estudo é financiado através do programa Horizon2010 que é liderado pela empresa EPICONCEPT que inclui 13 institutos europeus.

**Tipo de Estudo:** Observacional, multicêntrico, Europeu.

**Local:** Hospital S. José, Área da Medicina e Cirurgia.

### Apreciação:

Estudo de efectividade da vacina para Influenza em casos de infecção grave.

Objectivo: estimar a efectividade da vacina antigripal em gripe confirmada laboratorialmente em doentes hospitalizados com infecção grave.

Desenho do estudo: Comparar IRA (infecção respiratória aguda grave) com laboratório positivo para vírus da gripe com IRA grave com laboratório negativo para vírus da gripe (grupo 1 de controlo) e com indivíduos internados em enfermarias de cirurgia (grupo 2 controlo).

Duração do estudo: 3 anos com início em Novembro 2015

Local: Hospital de S. José (onde será feita a identificação dos casos e dos controlos, a recolha da informação e do exsudado faríngeo).

Critérios de inclusão: Doentes de todas as idades não institucionalizados e admitidos com infecção respiratória aguda grave e sem contra indicações para tomarem a vacina

Recolha de dados: Epidemiológicos, sinais e sintomas, co-morbilidades, registo de vacinas, resultado laboratorial para o tipo e subtipo de gripe são colhidos em entrevista ao próprio ou a familiar, do processo clínico e do registo de vacinas administradas através do SNS.

Tratamento de dados: Dados são introduzidos anonimizados em base de dados do INRJ e serão enviados para a equipa coordenadora (EPICONCEPT).

Os dados serão apresentados em artigos científicos, relatórios técnicos nacionais e internacionais.

Há verba própria para as análises laboratoriais (tipo e subtipo de vírus da gripe).

Existe autorização da Coordenadora da Área Médica, mas não da Área Cirúrgica nem dos coordenadores dos serviços onde se realizará o estudo.

O estudo da efectividade da vacina para Influenza em casos de infecção grave tem interesse.

É garantida a confidencialidade dos dados e não há custos acrescidos para os doentes nem para o Centro Hospitalar.

Tem parecer favorável da CNPD.

Os Serviços envolvidos serão indicados pelo Director Clínico, conforme acordo entre as partes.

**Conclusão:**

O estudo não levanta questões do ponto de vista ético, respeitando as normas de boa prática clínica, e está de acordo com a Declaração de Helsínquia e posteriores actualizações pelo que se emite parecer favorável à sua autorização/realização.

O Presidente da Comissão de Ética



(António Santos Castro, Dr)

Deliberação

- 1) Autorizada a realização do estudo.
- 2) Ao GID para dar seguimento.

NOTA DE SERVIÇO

Para: Exma. Sra. Dra. Teresa Magalhães, Vogal Executiva do Conselho de Administração

De: Filipa Cabral de Brito Serra, Administradora do Gabinete de Investigação e Desenvolvimento

06-01-2016

Assunto: Estudo Efetividade da Vacina Antigripal em contexto hospitalar – Projeto I MOVE +

Sobre o pedido do estudo em epígrafe (dossier em anexo) e conforme despacho do Sr. Coordenador do GID, Prof. Filipe Inácio, em anexo, propõe-se que o mesmo seja aprovado pelo Conselho de Administração.

Com efeito:

1. A Comissão de Ética para a Saúde também deu parecer favorável por unanimidade à realização do estudo, assim como o Sr. Prof. Filipe Inácio (ver em anexo);
2. O estudo tem uma dimensão europeia, é patrocinado pela união europeia e pelo INSA, pelo que se considera que será prestigiante para o CHS;
3. O estudo pretende avaliar a efetividade da vacina contra a infeção por vírus influenza dos genótipos A e B na população com pessoas com mais de 65 anos não institucionalizadas
4. Para a sua efetividade é preciso celebrar um acordo de parceria entre o INSA e o CHS (em anexo).
5. Neste acordo e na cláusula décima, o promotor reembolsará em 16 000 €, que pretende cobrir os custos com os testes laboratoriais e os profissionais de saúde. De acordo com a informação obtida telefonicamente com o Sr. Dr. Poças a distribuição será de 25 % para os serviços participantes, 25 % para o CHS e 50 % para os investigadores/profissionais envolvidos;
6. O investigador principal e coordenador do CHS é o Sr. Dr. José Poças e fará este estudo em colaboração com os serviços de Imuno-alergologia, de Urgência, UCI, Medicina Interna, Pneumologia, Ginecologia/Obstetrícia e o próprio serviço que dirige, bem como todos os outros serviços de internamento do HSB, com exceção do HOSO.

À consideração superior,

Filipa Cabral de Brito Serra

Despacho

Terei conhecimento.

À Sr. D. Teresa Magalhães

para:

1) Dar conhecimento

ao elemento do

GID e à CES

2) Dar conhecimento

ao Sr. Dr. Poças

e Sr. Prof. Filipe

Inácio, respetivo

Diretor do Serviço

de Imunoalergologia

3) Solicitar ao

responsável do

Projeto do INSA o acordo

com o CHS para o

CA: custeio

4) Marcar reunião

com o Serviço Financeiro

para estabelecimento do acordo

em 01/01/16

Assinatura: 01/01/16





AUTORIZAÇÃO N.º 6084/2015

## I. Pedido

O Instituto Nacional de Saúde Dr. Ricardo Jorge notificou à Comissão Nacional de Protecção de Dados (CNPD) um tratamento de dados pessoais com a finalidade de elaborar um “Estudo da Efetividade da Vacina Antigripal em contexto hospitalar – EVA Hospital”.

Trata-se de estudo que terá a duração de três anos e que tem como objetivo estimar a efetividade da vacina antigripal sazonal contra gripe confirmada laboratorialmente em doentes hospitalizados com infeção respiratória aguda grave.

Aos participantes no estudo será pedido que respondam a um questionário, bem como será colhida uma amostra do exsudado nasofaríngeo, para realização de análises laboratoriais.

O médico assistente, investigador no estudo, solicitará consentimento informado, cuja declaração será arquivada no processo clínico do doente.

Os dados serão recolhidos num caderno de dados no qual não há identificação nominal do titular, sendo aposto um código de participante no estudo. A chave desta codificação só pode ser conhecida do médico assistente.

Os destinatários são ainda informados sobre a natureza facultativa da sua participação e garantida confidencialidade no tratamento.

## II. Análise

A CNPD já se pronunciou na sua Deliberação n.º 227/2007 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios orientadores para o correto cumprimento da LPD, bem como as condições gerais aplicáveis ao tratamento de dados pessoais para a finalidade de estudos de investigação na área da saúde.

Porque em grande parte referentes à vida privada e também à saúde, os dados recolhidos pela requerente têm a natureza de sensíveis, nos termos do disposto no n.º 1 do artigo 7.º da LPD.

Em regra, o tratamento de dados sensíveis é proibido, de acordo com o disposto no n.º 1 do artigo 7.º da LPD. Todavia, nos termos do n.º 2 do mesmo artigo, o tratamento de dados da vida privada e de saúde é permitido, quando haja uma disposição legal que consagre esse tratamento de dados, quando por motivos de interesse público importante o tratamento for indispensável ao exercício das atribuições legais ou estatutárias do seu responsável ou quando o titular dos dados tiver prestado o seu consentimento.

Não estando preenchidas as duas primeiras condições de legitimidade, o fundamento de legitimidade só pode basear-se no consentimento dos titulares dos dados ou dos representantes legais, quando os titulares dos dados sejam incapazes.

Assim, é necessário o «consentimento expresso do titular», entendendo-se por consentimento qualquer manifestação de vontade, livre, específica e informada, nos termos da qual o titular aceita que os seus dados sejam objeto de tratamento (cf. artigo 3.º, alínea *h*), da LPD), o qual deve ser obtido através de uma “declaração de consentimento informado” onde seja utilizada uma linguagem clara e acessível.

Nos termos do artigo 10.º da LPD, a declaração de consentimento tem de conter a identificação do responsável pelo tratamento e a finalidade do tratamento, devendo ainda conter informação sobre a existência e as condições do direito de acesso e de retificação por parte do respetivo titular.



Os titulares dos dados, de acordo com a declaração de consentimento informado junta aos autos, apõem as suas assinaturas na mesma, deste modo satisfazendo as exigências legais.

Cabe ao Investigador assegurar a confidencialidade dos dados pessoais e da informação tratada, conforme o estatuído na alínea *g)* do artigo 10.º da Lei n.º 21/2014, de 16 de abril (Lei da investigação clínica).

O responsável declarou a existência de comunicação de dados a terceiros, mas apenas há transmissão de dados codificados, pelo que a mesma não se verifica.

A informação tratada é recolhida de forma lícita (artigo 5.º, n.º1 alínea *a)* da Lei n.º 67/98), para finalidades determinadas, explícitas e legítimas (cf. alínea *b)* do mesmo artigo) e não é excessiva.

O fundamento de legitimidade é o consentimento expresso do titular dos dados.

### III. Conclusão

Assim, nos termos das disposições conjugadas do n.º 2 do artigo 7.º, n.º 1 do artigo 27.º, alínea *a)* do n.º 1 do artigo 28.º e artigo 30.º da Lei de Protecção de Dados, com as condições e limites fixados na referida Deliberação n.º 227/2007, que se dão aqui por reproduzidos e que fundamentam esta decisão, autoriza-se o tratamento de dados *supra* referido, consignando-se o seguinte:

**Responsável pelo tratamento:** Instituto Nacional de Saúde Dr. Ricardo Jorge;

**Finalidade:** Estudo da Efetividade da Vacina Antigripal em contexto hospitalar – EVA Hospital”;

**Categoria de Dados pessoais tratados:** código do doente, idade, sexo, sinais e sintomas de síndrome gripal (febre, mal estar, mialgia, tosse, dor de garganta, dor de cabeça e dificuldade respiratória), resultado laboratorial de diagnóstico de gripe,



vacinação antigripal na época (data da vacinação e nome da vacina) e época passada, doenças crónicas; Índice de Barthel; Antiviral; resultados laboratoriais ao exsudado nasofaríngeo.

Entidades a quem podem ser comunicados: Não há.

Formas de exercício do direito de acesso e retificação: Junto do responsável.

Interconexões de tratamentos: Não há.

Transferências de dados para países terceiros: Não há.

Prazo de conservação: A chave de codificação dos dados do titular deve ser destruída um mês após o fim do estudo.

Dos termos e condições fixados na Deliberação n.º 227/ 2007 e na presente Autorização decorrem obrigações que o responsável deve cumprir. Deve, igualmente, dar conhecimento dessas condições a todos os intervenientes no circuito de informação.

Lisboa, 30 de junho de 2015

A handwritten signature in black ink, appearing to read 'Filipa', is written over a horizontal line.

Filipa Calvão (Presidente)

AUTORIZAÇÃO N.º 6082/2015

I. Pedido

O Instituto Nacional de Saúde Dr. Ricardo Jorge notificou à Comissão Nacional de Protecção de Dados (CNPD) um tratamento de dados pessoais com a finalidade de elaborar um estudo que pretende obter estimativas da efetividade da vacina sazonal e pandémica durante e após a época de gripe na população geral e nos indivíduos com 60 ou mais anos de idade (Projecto EUROEVA).

Trata-se de estudo que deverá realizar-se anualmente e que pretende a inclusão de indivíduos com sinais e sintomas gripais, que recorram a consulta de Medicina Geral num dos centros participantes.

Aos participantes no estudo será pedido que respondam a um questionário, bem como será colhida uma amostra do exsudado nasofaríngeo, para realização de análises laboratoriais.

O médico assistente, investigador no estudo, solicitará consentimento informado, cuja declaração será arquivada no processo clínico do doente.

Os dados serão recolhidos num caderno de dados em suporte papel. A informação codificada será enviada por correio expresso para o responsável pelo tratamento.

As amostras serão objeto da mesma codificação.

No “caderno de recolha de dados” não há identificação nominal do titular, sendo aposto um código de participante no estudo. A chave desta codificação só pode ser conhecida do médico assistente.

Os destinatários são ainda informados sobre a natureza facultativa da sua participação e garantida confidencialidade no tratamento.

## II. Análise

A CNPD já se pronunciou na sua Deliberação n.º 227/2007 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios orientadores para o correto cumprimento da LPD, bem como as condições gerais aplicáveis ao tratamento de dados pessoais para a finalidade de estudos de investigação na área da saúde. Porque em grande parte referentes à vida privada e também à saúde, os dados recolhidos pela requerente têm a natureza de sensíveis, nos termos do disposto no n.º 1 do artigo 7.º da LPD.

Em regra, o tratamento de dados sensíveis é proibido, de acordo com o disposto no n.º 1 do artigo 7.º da LPD. Todavia, nos termos do n.º 2 do mesmo artigo, o tratamento de dados da vida privada e de saúde é permitido, quando haja uma disposição legal que consagre esse tratamento de dados, quando por motivos de interesse público importante o tratamento for indispensável ao exercício das atribuições legais ou estatutárias do seu responsável ou quando o titular dos dados tiver prestado o seu consentimento.

Não estando preenchidas as duas primeiras condições de legitimidade, o fundamento de legitimidade só pode basear-se no consentimento dos titulares dos dados ou dos representantes legais, quando os titulares dos dados sejam incapazes.

Assim, é necessário o «consentimento expresso do titular», entendendo-se por consentimento qualquer manifestação de vontade, livre, específica e informada, nos termos da qual o titular aceita que os seus dados sejam objeto de tratamento (cf. artigo 3.º, alínea *h*), da LPD), o qual deve ser obtido através de uma “declaração de consentimento informado” onde seja utilizada uma linguagem clara e acessível.

Nos termos do artigo 10.º da LPD, a declaração de consentimento tem de conter a identificação do responsável pelo tratamento e a finalidade do tratamento, devendo ainda conter informação sobre a existência e as condições do direito de acesso e de retificação por parte do respetivo titular.



Os titulares dos dados, de acordo com a declaração de consentimento informado junta aos autos, apõem as suas assinaturas na mesma, deste modo satisfazendo as exigências legais.

Cabe ao Investigador assegurar a confidencialidade dos dados pessoais e da informação tratada, conforme o estatuído na alínea *g*) do artigo 10.º da Lei n.º 21/2014, de 16 de abril (Lei da investigação clínica).

A informação tratada é recolhida de forma lícita (artigo 5.º, n.º1 alínea *a*) da Lei n.º 67/98), para finalidades determinadas, explícitas e legítimas (cf. alínea *b*) do mesmo artigo) e não é excessiva.

O fundamento de legitimidade é o consentimento expresso do titular dos dados.

### III. Conclusão

Assim, nos termos das disposições conjugadas do n.º 2 do artigo 7.º, n.º 1 do artigo 27.º, alínea *a*) do n.º 1 do artigo 28.º e artigo 30.º da Lei de Protecção de Dados, com as condições e limites fixados na referida Deliberação n.º 227/2007, que se dão aqui por reproduzidos e que fundamentam esta decisão, autoriza-se o tratamento de dados *supra* referido, consignando-se o seguinte:

**Responsável pelo tratamento:** Instituto Nacional de Saúde Dr. Ricardo Jorge;

**Finalidade:** estudo que pretende obter estimativas da efetividade da vacina sazonal e pandémica durante e após a época de gripe na população geral e nos indivíduos com 60 ou mais anos de idade (Projecto EUROEVA);

**Categoria de Dados pessoais tratados:** código do doente, idade, sexo, sinais e sintomas de síndrome gripal (febre, mal estar, mialgia, tosse, dor de garganta, dor de cabeça e dificuldade respiratória), resultado laboratorial de diagnóstico de gripe, vacinação antigripal na época (data da vacinação e nome da vacina) e época passada, doenças crónicas (obesidade mórbida, diabetes, doenças cardiovasculares,



insuficiência cardíaca, doença respiratória crónica, doença hepática crónica, doença neuromuscular), se é profissional de saúde, co-habitante ou cuidador de crianças que tenham risco elevado de desenvolver complicações, cuja idade é 6 meses, gravidez e trimestre, hospitalizações nos últimos 12 meses, número consultas de medicina geral e familiar nos últimos 12 meses, número de anos de escolaridade, número de co-habitantes na unidade de alojamento, necessidade de assistência no banho e hábitos tabágicos; resultados laboratoriais ao exsudado nasofaríngeo.

**Entidades a quem podem ser comunicados:** Não há.

**Formas de exercício do direito de acesso e retificação:** Junto do responsável.

**Interconexões de tratamentos:** Não há.

**Transferências de dados para países terceiros:** Não há.

**Prazo de conservação:** A chave de codificação dos dados do titular deve ser destruída um mês após o fim do estudo, anualmente.

Dos termos e condições fixados na Deliberação n.º 227/ 2007 e na presente Autorização decorrem obrigações que o responsável deve cumprir. Deve, igualmente, dar conhecimento dessas condições a todos os intervenientes no circuito de informação.

Lisboa, 30 de junho de 2015

A handwritten signature in black ink, appearing to read 'Filipa', with a long horizontal stroke extending to the right.

Filipa Calvão (Presidente)