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ARTIGO ORIGINAL

Implementing an Influenza Vaccine Effectiveness Study in a Hospital Context in Portugal: The EVA Hospital Project

Implementação de um Estudo de Efetividade da Vacina Contra a Gripe no Contexto Hospitalar em Portugal: Projeto EVA Hospital

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Acta Med Port 2021 Jan;34(1):20-27 ▪ https://doi.org/10.20344/amp.13438

ABSTRACT

Introduction: The project 'Integrated Monitoring of Vaccines in Europe' aimed to measure seasonal influenza vaccine effectiveness against hospitalised adults, aged 65 years and over, with influenza. We describe the protocol implementation in Portugal.

Material and Methods: We implemented a test-negative design, targeting community-dwelling patients aged 65 years old and over hospitalised with severe acute respiratory illness. Patients were reverse transverse-polymerase chain reaction tested for influenza. Cases were those positive for influenza while others were controls. Most variables were collected using hospital medical records. Selection bias was evaluated by comparison with the laboratory influenza test requests database according to demographic characteristics. Crude, season-adjusted influenza vaccine effectiveness was estimated as = 1 – odds ratio, and 95% confidence intervals were obtained by conditional logistical regression, matched with the disease onset month.

Results: The recruitment rate was 37.8%. Most participants (n = 368) were female (55.8%) and aged 80 years old and over (55.8%). This was similar to values for potentially eligible severe acute respiratory illness patients (80 years old and over: 56.8%, female: 56.2%). The proportion of missing values was below 2.5% for 20 variables and above 5% (maximum 11.6%) for six variables. Influenza vaccine effectiveness estimates were 62.1% against AH1pdm09 (95% confidence intervals: -28.1 to 88.8), 14.9% against A(H3N2) (95% confidence intervals: -69.6 to 57.3), 43.6% against B/Yam (95% confidence intervals: -66.2 to 80.8).

Discussion: Given the non-existence of a coded admission database in either participating hospital the selection of severe acute respiratory illness due to clinical features was the feasible one. These results are only valid for the older adult population residing in the catchment area of the two participating hospitals who were admitted to a public hospital with severe influenza or SARI symptoms.

Conclusion: Despite the low participation rate, we observed comparable characteristics of participants and eligible severe acute respiratory illness patients. Data quality was high, and influenza vaccine effectiveness results were in accordance with the results of meta-analyses and European season-specific estimates. The final sample size was low, which inhibited obtaining estimates with good precision.

Keywords: Influenza, Human; Influenza Vaccines; Portugal; Respiratory Tract Infections; Reverse Transcriptase Polymerase Chain Reaction

RESUMO

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

Material e Métodos: Implementou-se um estudo com desenho caso-controlo teste negativo. A população-alvo foram indivíduos com idade superior a 65 anos, hospitalizados com doença respiratória aguda grave. Os doentes foram testados para gripe por *reverse transverse-polimerase chain reaction*. Foram considerados casos aqueles com resultado positivo; os restantes foram controlos. Os dados foram obtidos através de registo clinicos. 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 em 1 – *odds ratio* por regressão logística condicional, emparelhada para o mês de início da doença.

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

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Recebido: 14 de janeiro de 2020 - Aceite: 14 de setembro de 2020 | Copyright © Ordem dos Médicos 2021

Discussão: Dada a inexistência de uma codificação em base de dados de admissão em qualquer um dos hospitais participantes, a abordagem de identificação e casos clínicos de doença respiratória aguda grave foi a exequível. Estes resultados são válidos para a população idosa residente na área de abrangência dos dois hospitais participantes que foram internados em um hospital público com gripe grave ou sintomas de doença respiratória aguda grave.
Conclusão: Apesar da baixa taxa de participação, observámos 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-análises e estimativas europeias. A reduzida dimensão da amostra impediu a obtenção de estimativas mais precisas.
Palavras-chave: Gripe; Infecções Respiratórias; Portugal; Reacção em Cadeia da Polimerase Via Transcriptase Reversa; Vacina contra Gripe

INTRODUCTION

In recent years, estimating the influenza vaccine effectiveness (IVE) has been of extreme importance in order to evaluate the benefits of the influenza vaccine in reducing the incidence of 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.[1,2] Older adults, aged 65 years and over, are an important target of these studies, considering the expected effectiveness of the vaccine in not only reducing the incidence of the infection but also reducing related hospitalisations and even death.[3,4]

By using the primary care setting, it was possible to estimate 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 former, despite not being significant.[5,6] The extended protection provided by the influenza vaccine against severe cases that require hospitalisation was expected to be greater. Severe cases that require hospitalisation comprise an average of 64% of influenza-related pneumonia and influenza hospitalisations each year.[7]

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.[8,9] A number 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.[8] Other IVE studies have also been implemented with the common ground of the existence of hospital-based surveillance systems.[10]

In Portugal, the influenza vaccine has been available free of charge to the population aged 65 years and over since 2012. Approximately 75% of the vaccinated older adults received their vaccinations in primary care centres.[11] Vaccines that are administered at the health centre are registered in electronic vaccination registries and made available on the Health Data Platform, which can be accessed by healthcare professionals using their individual National Health Service user credentials. As such, 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 Integrated Monitoring of Vaccines in Europe (IMOVE+ project), a study was designed and implemented in Portugal (EVA Hospital study). The aim of this study is to describe the implementation in Portugal of the IVE study targeting the population 65 years and over during three consecutive seasons (2015/16 to 2017/18) and evaluation of its internal and external validity in two Portuguese hospitals.

MATERIAL AND 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 over, hospitalised with SARI in one of the participating hospitals and wards, without contraindication for the influenza vaccine.

Following the TND IVE hospital protocol,[9] patients were eligible for participation according to SARI definition: hospitalised (over 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, onset of SARI symptoms more than 48 hours after admission (i.e., nosocomial SARI), positive test for influenza before recruitment within the season (i.e., previous influenza) and antiviral treatment between symptom onset and swab testing. Exclusion 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 seven 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. The diagnosis of influenza diagnosis was confirmed in 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 medical conditions, number of hospitalisations for acute exacerbation of chronic diseases in the previous 12 months and number of GP / family physician visits in the previous three months, smoking status, antiviral administration, pneumococcal vaccination status and laboratory results. All data collection was performed by a physician, 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, with double data entry.

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[11] and a proportion of positive cases 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, in order to estimate an odds-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 seasons 2016/17 and 2017/18 was computed considering participants and the number 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 test 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 were 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 lasted less than 24 hours. The total number of potentially eligible SARI patients was 843 (Fig. 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%.

The weekly distribution of participants of the 2016/17 and 2017/18 seasons (n = 292) and all potential SARI patients (n = 1423) [Appendix 1, Fig. S1 (see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13438/Appendix_01.pdf)] 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.

Descriptive data

Considering the three seasons, 368 SARI patients accepted participating 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 the swab (41 out of 66).

This resulted in 302 SARI patients being included in the analysis. From these, 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 to the overall analysis. The weekly distributions

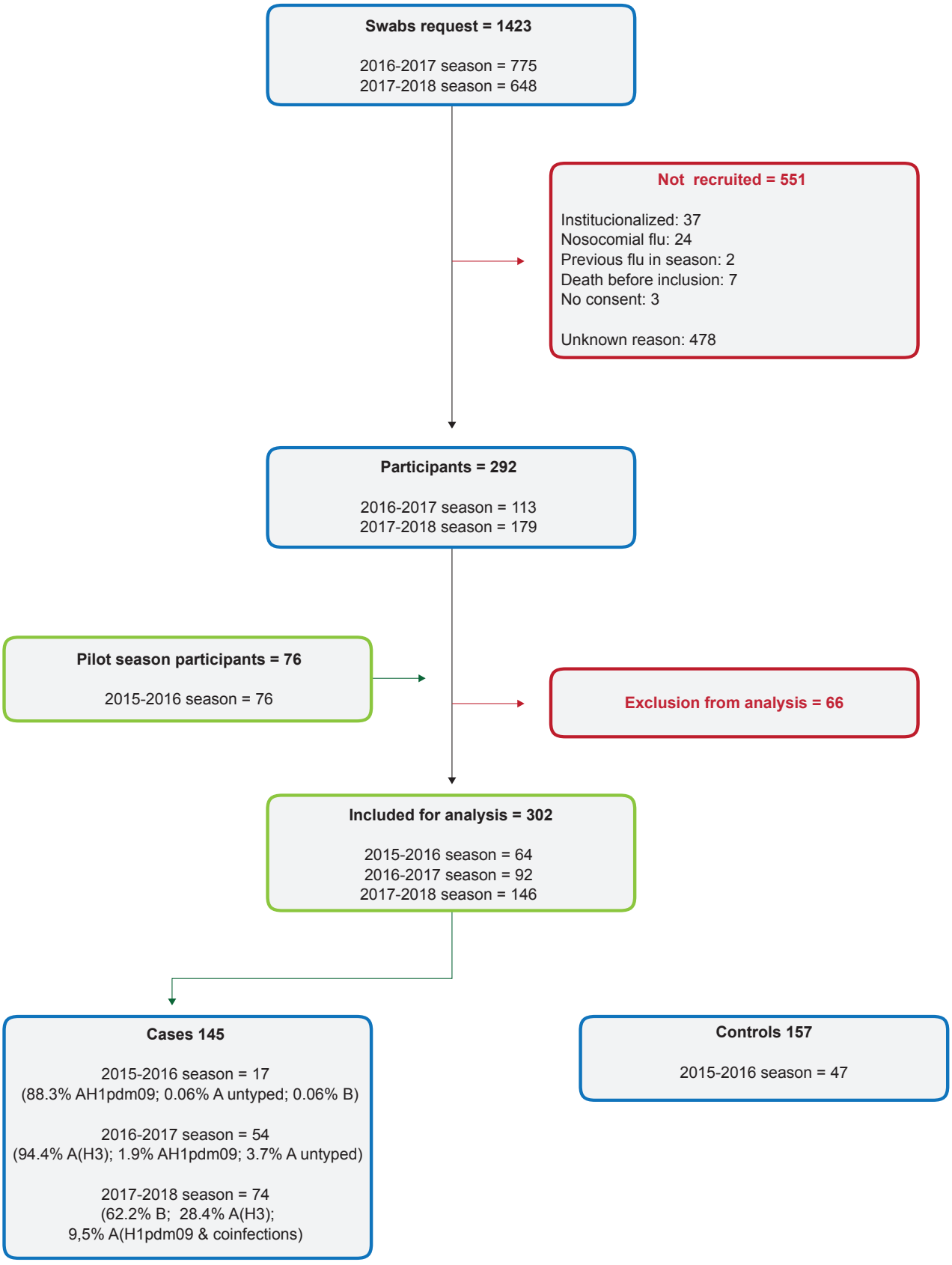

Figure 1 – Flow diagram of EVA Hospital participants

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	%	
Sex					**0.7918**
Female	800	56.2	163	55.8	
Male	623	43.8	129	44.2	
Age group					**0.5982**
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

of cases and controls [Appendix 1, Fig. S1 (see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13438/Appendix_01.pdf)] 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 pneumococcal 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.

Main results

Crude IVE point estimates indicate that the vaccine reduced the risk of SARI due to influenza during the seasons in the study by 32.1% (95% CI: -18.6 to 61.1) (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.

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 the generalisability of results.[12] 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 during 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.[13]

This comparable pattern was observed in both the sociodemographic characteristics of 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 estimates. 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.[14,15] These features combined with a specific outcome such as laboratory-confirmed influenza, reassure the assessment of unbiased IVE estimates.[12] 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[12] 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 ensure minimised selection bias in the context of the SARI identification approach used in the EVA Hospital project. It should be stressed 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[16] 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 coded admission database in either participating hospital.

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

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[a]
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 months, median (total)	2.6	1.0 (138)	1.0 (156)	0.723[a]
Hospitalizations , median (total)	0.0	0.0 (145)	0.0 (157)	0.596[a]
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
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 [a] Mann-Whitney test
* Defined as if the patient has difficulty doing at least one of the actions of the Barthel Index

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 admission in private hospitals.

Overall eligibility criteria were assessed for approximately two-thirds of the individuals with a swab test 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

Table 3 – Influenza vaccine effectiveness 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%	-56.0 to 85.8

* conditional logistic regression model, match for week of onset and season
OR: odds-ratio; IVE: influenza vaccine effectiveness; 95% CI: 95% confidence interval

the recruitment (participation) rate is the proportion of participants out of the total number of individuals eligible for the study (all swabbed individuals according to the laboratory database of each hospital), 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.[8]

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 pertains to the severity of the outcome (hospitalisation) that makes characteristics more homogeneous; therefore, it may be due to common risk factors and may not be influenza-specific.

The overall quality of the 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 PDS. The access to this platform was extremely valuable for collecting and validating patient information. This platform was easily accessed by healthcare professionals and included vaccination data (present and past season influenza and pneumococcal vaccine). All the influenza vaccines that were administered in the health centre were registered in this database. For the population aged 65 and over who lived in the catchment area of the Lisbon hospitals, the proportion of participants vaccinated in the health centre was 68% in the 2015/16 season and 67% in the 2017/18 season.[17,18] 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 advantageous for compiling an individual health record. On the other hand, given that the information is not structured and relies on reporting by a healthcare 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 increase in the amount 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 expanding. Data at the hospital level was collected prospectively, and relevant data was collected by the participating physicians, who were trained for data collection.

Concerning laboratory results, they were obtained using high-sensitivity and high-specificity RT-PCR,[19] 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 the 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.[20] 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 the 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.

ACKNOWLEDGEMENTS

The authors would like to acknowledge all the EVA Hospital participants and MD students in both hospitals for their assistance in data gathering and validation.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This work is part of I-MOVE+ (Integrated Monitoring of Vaccines in Europe) project that received funding from the European Union's Horizon 2020 research and innovation programme [grant agreement number 634446].

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