European Union

I-MOVE+

Measuring influenza vaccine effectiveness against pneumococcal pneumonia using the screening method

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WP nr	3
Deliverable nr	3.7
Title of the deliverable	Role of influenza on IPD and/or CAP
Date	1 october 2018

Acronyms

CATI	Computer Assisted Telephone Interview
ECDC	European Centre for Disease Prevention and Control
ECOS	*Em Casa Observamos Saúde*
HC	Health Centre
I-MOVE	Influenza Monitoring Vaccine Effectiveness
IPD	Invasive Pneumococcal Disease
IVE	Influenza Vaccine Effectiveness
OR	Odds Ratio
PCV13	13-valent Pneumococcal Conjugated Vaccine
PP	Pneumococcal Pneumonia
PPSV23	Pneumococcal Polysaccharide Vaccine
TND	Test-negative Design
VC	Vaccination Coverage

1. Background

Vaccination has been one of the main measures to mitigate influenza impacts and its role in reducing the risk of influenza infection and some of its complications is well known (1).

Influenza viruses can induce pneumonia and also favour bacterial co-infections and secondary bacterial infections. The pathogenic mechanism is multifactorial involving host susceptibility and transmission between close contacts, respiratory epithelial damage, changes in airway functions with up-regulation/exposure of specific receptors; or increased level of proinflammatory cytokines and vascular permeability of the pulmonary tract allowing bacterial invasion of the blood (2-6). While these mechanisms could favor supra-infections with other bacteria, pneumococci exhibit a special synergism with influenza and other respiratory viruses. First, the increase in carriage prevalence during the winter season concurs with the circulation of influenza and other respiratory viruses (7,8) mainly due to increased pneumococcal acquisition (9) and density in nasopharynx (10). Second, the incidence and severity of pneumococcal pneumonia (PP) increase during the winter season (5), being the invasiveness of pneumococcal serotypes mainly related to the carriage density and acquisition. As consequence, there is plausibility that influenza vaccination may also protect against pneumococcal outcomes.

In Portugal, individuals with 65 years of age and more are part of the target group for influenza vaccination (11). Data from the vaccine coverage monitoring system indicates that vaccination coverage in elderly has been approximately 50% (12). Since 2012, influenza vaccination is offered free of charge to the elderly (≥ 65 years) at the National Health System without prescription. Individuals can also be vaccinated in a pharmacy if the person has a medical prescription. During the 2015/16 season around 75% of the vaccinated elderly received the vaccine in their Health Centre (HC) (14). This percentage varied between heath regions and in Lisbon (reference population of this study) only 68% of elderly referred been vaccinated in their HC (unpublished data). Each season, Portuguese national influenza vaccination campaign starts in October (14) and most elderly were vaccinated before the end of December (15).

Portugal, alongside with other European countries has been using the screening method to estimate seasonal influenza vaccine effectiveness (IVE). This method was first used in the 2009/10 season and was implemented during the following three seasons. The results obtained from its study design, when compared to the test-negative design, were less precise and more likely to be biased (16). According to Orenstein et al (17), the screening method only provides a rough guide of the VE point estimates and for this reason, it should not be relied upon for precise estimates. Nevertheless, it can be used to easily monitor VE, given its potential advantage in terms of timeliness and low resources needs. We considered the screening method as a potential design to pilot within the I-MOVE+ to estimate the influenza vaccine effectiveness against two specific outcomes: Invasive Pneumococcal Disease (IPD) and PP.

The aim of this study was to evaluate the feasibility of using the screening method to estimate the influenza vaccine effectiveness against IPD and PP using hospital and surveillance data.

2. Objective

The main objective was to measure in the community dwelling elderly population (aged ≥65 years) the direct effect (effectiveness) of influenza vaccine against:

i. Pneumococcal pneumonia (PP);
ii. Invasive pneumococcal disease (IPD).

3. Methods

3.1 Study design

Screening method that compares the proportion of cases who were vaccinated (**Cases**) with the proportion vaccinated in the population from where cases have arose (**Study reference population**).

3.2 Study population

The study population consisted of the community dwelling individuals aged ≥65 years old hospitalized in two central hospitals in Lisbon (*Centro Hospitalar Lisboa Norte* and *Centro Hospitalar Lisboa Central*) during the study period.

Given that hospitals enrolled in this study are located in Lisbon the reference population corresponded to the non-institutionalized population resident in Lisbon region.

3.3 Study period

Cases	From week 40/2016 to week 25/2018
Reference population (ECOS sample)	From week 11/2016 to week 19/2016

Only cases admitted to participating hospitals at least 14 days after the beginning of the vaccination campaign during influenza circulation period (week 42/2016 to week 20/2017; 43/2017 to week 19/2018) were considered.

3.4 Outcomes

Outcomes of interest were PP and IPD as defined below.

3.5 Definitions

Pneumococcal Pneumonia Case

A PP case was defined as a hospitalized individual (more than 24 hours) with pneumonia that had a positive sample (urine, blood, sputum, other) for *Streptococcus pneumoniae*.

IPD cases were defined as a hospitalized individual (more than 24 hours) that had a positive result for *Streptococcus pneumoniae* from a sterile fluid.

Reference Population

Reference population data were obtained from a sample of approximately 1000 households stratified by region selected from a dual sampling frame – using random digit dialing mobile and landline phones (ECOS sample) (13). This study has been monitoring the vaccine coverage in mainland Portuguese population since 1998 (18,19).

3.6 Sampling

Case identification

Cases were identified from two hospitals using two different strategies. For one hospital (*Centro Hospitalar Lisboa Norte*), PP cases were identified from the hospital discharge database. All patients that had a hospitalization episode which primary diagnosis was coded as 481,486 (pneumococcal pneumonia and unspecified pneumonia) and 510 (empyema) were selected. Medical records from all patients were reviewed by a medical doctor to identify possible exclusion criteria and to confirm laboratorial results. Data collection was performed using a standard paper form.

Regarding to the other hospital (*Centro Hospitalar Lisboa Central*), PP cases were selected among Severe Acute Respiratory Infection (SARI) patients enrolled for EVA hospital Study (20). SARI cases were considered as PP cases if they had a chest X-Ray compatible with pneumonia and a positive urinary antigenic test (or hemoculture) for *Streptococcus pneumoniae* (Annex 1).

Case exclusion criteria

Cases were excluded if they:

- were institutionalized;
- were admitted to the hospital out of the influenza circulation period;
- had registry of nosocomial infection;
- were not resident in Lisbon Region;

- didn't have registry of *Streptococcus pneumoniae* infection laboratorial confirmed;
- were vaccinated against seasonal influenza less than 15 days before the admission.

3.7 Exposure (Vaccination)

Vaccination status definition for cases

Cases were considered as vaccinated against influenza if they were vaccinated in the respective season until 14 days before hospitalization.

Ascertainment of vaccination in cases

Ascertainment was made using medical and vaccination registries. The vaccination history included date of administration (when available). Data collection was performed by a medical doctor through consultation of hospital and vaccination registries.

Vaccination coverage in reference group

The vaccine coverage in the study reference population was collected using the ECOS sample. In each interviewed household, one individual aged 18 or more years old provided information on his/her vaccination status and on the vaccination status of the rest of the household elements. For validation purposes, individuals were asked if the inoculation was through a "shot". The vaccination history included month of administration.

3.8 Other variables collected

Chronic conditions

Cases were considered as being chronically ill if two or more chronic conditions (cardiovascular disease, chronicle respiratory disease, oncological and hematological diseases, other immune deficiency conditions) were registered in the hospital records.

For the ECOS sample individuals were also considered as being chronically ill if they reported had been diagnosed (by a health professional) with at least two of the conditions included in the interview questionnaires (13).

Pneumococcal vaccines

Pneumococcal polysaccharide vaccine (PPV23) and 13-valent pneumococcal conjugated vaccine (PCV13) uptake was also collected only for cases using medical records and vaccination registry.

Smoking and alcohol

Smoking and alcohol abuse were collected only for cases using medical records.

3.9 Source of information

Table 1: Summary of data sources for cases and for reference population

Study	Standardised questionnaire	Laboratory results	Patient medical records	Vaccination status
Cases	No	Yes	Yes	Registry
Reference population	Yes	No	No	Self report/proxy

3.10 Data collected, management and validation

Full description of data collected, management and validation was described elsewhere for ECOS sample (13). A summary of collected data is presented in Table 2 and data dictionary of variables collected for cases is presented in Annex 2.

Table 2: Summary of data collected, management and validation in cases and in the reference population (ECOS sample).

	Cases	Reference population
Data collected	• Sociodemographic data (sex, age), • Influenza vaccination status in the season, • Smoking history, • Alcohol abuse, • Chronic conditions, • PCV13, PPSV23 vaccination status • Laboratorial results, Data collected was performed using a standardized paper form	• Sociodemographic data (sex, age), • Chronic conditions, • Influenza vaccine uptake 2015/16 season, • Intention of being vaccinated next season
Data management	Data entry was performed on a Microsoft Excel Database by typing in the answers from the paper form.	CATI survey was conducted and the database was validated and analyzed by the Department of Epidemiology at INSA.
Data validation	All cases were checked for missing values and inconsistencies. Data clarification and information recovery was made through medical registries checking.	Database validation was performed for each variable trough the identification of impossible values and inconsistencies identification. These inconsistencies were validated with the interviewer and/or with the participant via a new phone contact.

***Notes*:** PPSV23: pneumococcal polysaccharide vaccine; PCV13: 13-valent pneumococcal conjugated vaccine; CATI: Computer assisted telephone interview; INSA: Instituto Nacional de Saúde Doutor Ricardo Jorge

3.11 Statistical Analysis

Descriptive analysis

Cases and the study reference population were described by demographic characteristics and vaccination status.
Given its complex sample nature, design adjusted Rao–Scott version of Pearson's chi-square was used for association studies in the ECOS sample (21).

Measure of effect

IVE was estimated by comparing the proportion of vaccinated PP cases to the vaccine coverage in the study reference population using the Orenstein formula (22):

$$VE = \frac{PPV - PCV}{PPV(1 - PCV)}$$

in which PPV is the vaccine coverage in the reference population, and PCV is the vaccine coverage among Cases. Ninety five percent confidence intervals (95%CI) for IVE were computed using the Farrington method (23).

Stratified analysis

Analysis was stratified according to the availability of vaccination coverage in the reference group:

- Age groups (65-79 years and ≥80 years);
- Chronic conditions (< 2 chronic conditions and ≥ 2 chronic conditions).

Statistical analysis was performed using STATA version 13.

3.12 Ethical issues and data protection

ECOS panel was authorized by the National Data Protection Committee. Data collection regarding to cases were approved by the Ethical Committee of the National Institute of Health.

4. Results

4.1 Vaccination coverage in the reference population

According to the results of ECOS survey (24,25), the vaccine coverage in 2015/16 season for the Portuguese population aged 65 years or more was 50.1% (95%CI: 42.1-58.1) (13).

The majority of the individuals were vaccinated at the HC (60.4%; 95%CI: 49.1%; 70.6%) and during October (58.4%; 95%CI: 49.1%; 67.0%). Restricting to our reference population (Lisbon), the percentage of vaccinated at the HC was 68.0%. Vaccine coverage for the elderly population shown in table 3 revealed no statistically significant differences between regions.

Table 3: Influenza vaccine coverage (%) in the Portuguese mainland population and region

	%	95%CI	p-value*
North	44.4	(27.5; 62.6)	
Centre	53.1	(39.8; 66.0)	
Lisbon (study reference population)	**52.3**	**(37.6; 66.6)**	0.4374
Alentejo	51.7	(39.9; 63.3)	
Algarve	55.7	(44.4; 66.5)	
Portugal Mainland	50.1	(42.1; 58.1)	

* design-adjusted Rao–Scott version of Pearson's chi-square

4.2 Description of cases

Given the sampling strategy used, all selected cases had a pneumonia presentation some of them PP had a positive hemoculture for *Streptococcus pneumonia being* possible to classify as IPD. However, given the number of cases, PP cases considered in this analysis included invasive and non-invasive pneumonia.

Of 41 PP cases enrolled, 8 (19.5%) met at least one exclusion criteria, and the final sample of cases comprised 33 individuals. In all cases, laboratorial tests were performed for etiological diagnosis (urinary *Streptococcus pneumoniae* antigens identification, hemoculture, sputum culture or bronchoalveolar lavage culture).

Table 4 presents the description of selected PP cases. Comparing to the reference population, cases had a higher percentage of males and had a higher percentage of individuals chronically ill. Vaccine coverage was higher among the reference population.

Table 4: Description of pneumococcal pneumonia cases and Reference population

	PP	Reference Population
Age, mean (N)	75.8 (33)	75.6 (73.7; 77.6)
65-79 years, % (n/N)	63.6 (21/33)	72.1 (56.4; 83.8)
≥80 years, % (n/N)	36.4 (12/33)	27.9 (16.2; 43.6)
Sex, male % (n/N)	42.4 (14/33)	36.7 (29.4; 44.6)
Smokers, % (n/N)	45.0 (9/20)	NA
Alcohol abuse, % (n/N)	16.7 (1/6)	NA
≥ 2 chronic conditions , % (n/N)	75.8 (25/31)	45.3 (31.5; 59.9)
Seasonal influenza vaccine, % (n/N)	36.4 (12/33)	52.3 (37.6; 66.6)
PPSV23, % (n/N)	16.7 (5/30)	NA
PCV13, % (n/N)	9.7 (3/31)	NA

Notes: PP: pneumococcal pneumonia; NA: not available; PPSV23: pneumococcal polysaccharide vaccine; PCV13: 13-valent pneumococcal conjugated vaccine

4.3 Vaccine coverage

Overall VC in the reference population was higher than in cases indicating a potential protective effect of the influenza vaccine against PP (36.4% vs 52.3%) (Table 5).

Crude IVE estimate was 47.9% (95%CI: -5.9%; 74.4%) against PP. As no data on PPSV23 and PCV13 was available for the reference population, restricting analysis to those unvaccinated against *Streptococcus pneumoniae* was not possible.

Table 5: Influenza vaccine coverage and effectiveness (%) in the study reference population and in pneumococcal pneumonia cases

	PP (v/n)*		Reference Population [95%CI]
Vaccine coverage (%)	36.4	12/33	52.3 [37.6;66.6]
Vaccine effectiveness	**47.9 [-5.9; 74.4]**		
Vaccine coverage (%) 65-79 years	38.1	8/21	49.0 [33.0; 65.3]
Vaccine coverage (%) ≥80 years	33.3	4/12	60.7 [30.2; 84.7]
Vaccine coverage (%) <2 chronic conditions	37.5	3/8	41.6 [22.6; 63.5]
Vaccine coverage (%) ≥ 2 chronic conditions	36.0	9/25	65.2 [45.8; 80.5]

Notes: PP: pneumococcal pneumonia; *vaccinated/total of cases

5. Discussion

According to the screening method results, crude influenza vaccine effectiveness against pneumococcal pneumonia in hospital settings in 2016/17 and 2017/18 seasons was 47.9% (95%CI: -5.9%; 74.4%). The point estimate value is higher that reported in other study (31.7%; CI: 0.6% to 53.1%), but our results had low precision and were not statistically significant (26).

Given the low to moderate IVE against influenza estimated in the studied seasons, using the test negative design the screening method as well (27,28), we consider not plausible such high IVE against PP. But, it may indicate some level of protection of the influenza vaccine against pneumococcal pneumonia, which is in line with the hypothesis of risk of bacterial co-infections or secondary infections after an *Influenza* infection. Pneumococci synergism with *Influenza* and other respiratory viruses is well known, being mediated by the increase in pneumococcal acquisition (9) and density in nasopharynx (10) during the circulation of influenza and other respiratory viruses.

However several limitations of the study imposed precautions on results interpretation. Differences in chronic conditions and pneumococcal vaccination status between cases and the reference population could be an important source of bias as the influenza vaccination is not independent from the pneumococcal vaccination. Due to small sample size the adjustment for potential confounders was not possible and since no information regarding to pneumococcal vaccines (PPSV23 or PCV13) was collected for the reference population it was not possible to restrict analysis to those unvaccinated with any pneumococcal vaccine.

Another limitation of the screening method, as used here, is the fact that the vaccine coverage was assumed as known. However, it was also obtained from a population sample, so the variance of this estimate should be included in the 95% confidence interval VE estimate. Additionally, the chosen reference population (community dwellings aged 65 years and more) could not represent the group of selected patients. However, using the influenza vaccine coverage achieved in 2015/16 might not be an important source of bias as the influenza vaccine coverage in elderly has been around 50% in last years, with no significant yearly changes (29).

Since 2018, an universal vaccination registry replaced local vaccination registries, comprising all influenza vaccines inoculated in other places than in public HC. Thus, the error on influenza vaccination status on cases, due to the high percentage of elderly vaccinated out of HC that didn´t have any vaccine registered, should be lower than previously reported (30). However, as we didn´t get access to the information regarding to the site of the vaccination on cases, this error was not possible to quantify.

Given the growing interest on the role of influenza and influenza vaccine on pneumococcal disease, it seems necessary to continue to monitor IVE against influenza complications, particularly IPD and PP,

to support public health actions. However, we considered that different methods might be used, due to the bias that cannot be controlled by using the screening method to measure the IVE against the proposed outcomes.

Acknowledges

Carvalheira Santos, Conceição Junqueira, Ana Piteira, Maria José Pereira, Paula Pinto, Cristina Bárbara, Susana Sanches, Rita Corte-Real, António Panarra.

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7. Annexes

ANNEX 1: Selection of pneumococcal pneumonia cases among severe acute respiratory infection cases (11 pages)

1 Background

The feasibility study performed in Portugal in 2015/16 and 2016/17 seasons to estimate pneumococcal conjugated vaccine effectiveness in elderly showed that the primary care setting is not a suitable to identify and select pneumonia cases, as elderly population is preferentially attended at hospital level (1). Taking advantage of the established hospital network in Portugal to estimate influenza vaccine effectiveness (IVE) against hospitalized influenza (2), during the 2017/18 we proposed to test all Severe Acute Respiratory Infection (SARI) cases selected for EVA Hospital Study for *Streptococcus pneumoniae*. The pneumococcal pneumonia (PP) selected cases contributed to estimate the IVE against pneumococcal pneumonia using the screening method.

1.1 Objective

The objective of this study was to assess the feasibility to select PP cases from the SARI cases selected for EVA Hospital.

2 Methods

2.1 Study population

The study population comprised community-dwelling individuals aged 65 years and above with no contra-indication for influenza vaccination and hospitalized with SARI in one of the hospitals enrolled in EVA Hospital study (*Centro Hospitalar Lisboa Central* (CHLC)).

2.1.1 Participating Hospitals

CHLC is located at Lisbon district and its catchment area has about 362 016 inhabitants (17% of which aged 65 more years). For EVA Hospital study, all the internal medicine wards of four hospitals have participated in selecting SARI patients. The 10 participating wards had a total of 413 beds (than can be upgraded to 458 during contingency periods).

2.2 Study period

SARI patients were selected since week 47/2017 to week 17/2018.

2.3 Outcome of interest

The outcome of interest was PP in hospitalized patients with SARI and aged 65 years and above.

PP cases was defined as any SARI hospitalized case that had a thoracic radiography compatible with pneumonia and had a positive urinary antigenic test for *Streptococcus pneumoniae.*

2.1 Exposure

The exposure of interest was been vaccination against seasonal influenza within the 2017/18 season.

2.1.1 Definition of vaccination status and ascertainment

An individual was considered vaccinated against seasonal influenza if the vaccination occurred more than 14 days before SARI symptoms onset. Inoculation with the 2017/18 WHO approved seasonal influenza vaccine was ascertained by the health professional, by consultation of the vaccination registries. If vaccination registry was not available or individual data were not registered, an interview of the patient or his relatives was performed to collect vaccination data.

2.2 Case selection and sampling

2.2.1 Definition of SARI patients

A patient with SARI (3) was defined as an individual with at least one systemic symptom (fever, myalgia, malaise, headache and general deterioration) and one respiratory symptom (cough, sore throat and shortness of breath) and requiring hospital admission.

A hospitalised patient was defined as a patient who was admitted to the participating hospitals and hospitalised for at least 24 hours during the study period.

2.2.2 Inclusion and exclusion criteria

SARI patients were eligible if they met SARI definition and accepted to participate in the study. Written informed consent was collected by the health professional that approached the patient. Patients were excluded if they were unable to communicate. Other exclusion criteria were:

- contraindication for influenza vaccine;
- SARI onset more than 48 hours after admission at the hospital;
- institutionalization;
- influenza vaccine uptake less than 15 days of symptoms onset;
- previous pneumonia during 30 days previous to symptoms onset.

2.3 Source of information

Clinical data were collected using a standardised questionnaire filled by the medical doctor at hospital ward. Data sources included:

- hospital medical records and Health Data Platform
- interview with patient or his/her family
- vaccination registry
- hospital and National Institute of Health (INSA) laboratories

2.4 Variables collected

Table 1. Other variables collected

Variable	Definition
Chronic conditions	• diabetes, if treated for insulin-dependent or non-insulin-dependent diabetes; • cardiovascular disease (myocardial infarction, angioplasty, coronary artery bypass surgery, stroke, transient ischemic attacks, treated hypercholesterolemia, treated hypertension); • chronic pulmonary disease (asthma, chronic bronchitis, bronchopulmonary dysplasia, cystic fibrosis); • invasive pulmonary disease • chronic renal diseases (chronic renal failure); • rheumatologic disease • hematologic cancer • Non-hematologic cancer • Dementia • Stroke • Cirrhosis • Congenital or Acquired Immunodeficiency (conditions that suppress the immune function due to underlying disease and/or therapy – e.g. people receiving chemotherapy, HIV infection); and • obesity (IMC>=30) • nutritional deficiencies, anaemia.
Pneumonia	Previous pneumonia diagnosis during the 30 days before the symptoms onset.
Respiratory tuberculosis	Personal history of respiratory tuberculosis.
Antibiotics	Antibiotics use during the 30 days before the symptoms onset.
Smoking	Smoking history was collected and coded as follows: never-smoker, former smoker (stopped smoking at least one year before inclusion in the study), current smoker.
Previous vaccinations	Vaccination against seasonal influenza in the current (2017/18) and previous season (2016/17) and pneumococcal vaccinations (PPV23 and PCV13) and date of each vaccine uptake
Demographic variables	Sex, date of birth, date of hospital admission

Notes: PPSV23: pneumococcal polysaccharide vaccine; PCV13: 13-valent pneumococcal conjugated vaccine

2.5 Laboratorial methods

Urine samples were tested using an immunocromatographic commercial test kit (Alere BinaxNow *Streptococcus pneumoniae* antigen Card) that uses specific polyclonal antibodies against the C-polysaccharide moiety of *Streptococcus pneumoniae* for the rapid detection of *S. pneumoniae* antigen in urine, according manufacturers´ instructions. Sensibility and specificity estimates for pneumococcal community acquired pneumonia are 75 % and 95 % (4). Samples were tested at Hospital or at the National Reference Laboratory. Decision where sample were tested was carried out by patient´s medical doctor, accordingly the urgency of the result for the individual case management. Samples transportation to the National Reference Laboratory was refrigerated and daily performed. Non-urgent results were communicated to patient´s medical doctor within 24 hours.

Streptococcus pneumoniae urinary antigen-positive samples were further analysed for the detection of 24 serotype-specific pneumococcal antigens (capsular polysaccharides), including those covered

by the 13-valent pneumococcal conjugate vaccine (serotypes 1, 2, 3, 4, 5, 6A, 6B, 7B, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F), by means of a collaboration established between the National Reference Laboratory in Portugal and the Department of Bacterial Surveillance and Response, Centre for Infectious Diseases Research, Diagnostics and Screening from the Centre for Infectious Diseases Control of the National Institute for Public Health and the Environment in the Netherlands (RIVM) . This detection of specific urinary antigens was conducted by RIVM using an in-house, unpublished, inhibition multiplex immunoassay using the Bioplex technology (Luminex), adapted from Elberse et al (5) to detect at least 10ng/ml of polysaccharide per ml of urine for the 24 serotypes mentioned above.

2.6 Ethical Issues

The informed consent of 2016/17 EVA Hospital study was adapted for the 2017/18 season to include information regarding to the additional data needed.

The study protocol was approved by the Ethical Committee of the National Institute of Health.

3 Results

From 165 patients recruited within EVA Hospital that meet the inclusion criteria, 120 cases performed a urinary antigenic test for *Streptococcus pneumoniae*, which correspond to a participation rate of 72.7%. One patient that had a positive hemoculture for *Streptococcus pneumoniae* was also included in the sample, increasing the initial sample to 121 SARI cases.

Figure 1 represents the selection algorithm followed in respect of the exclusion criteria.

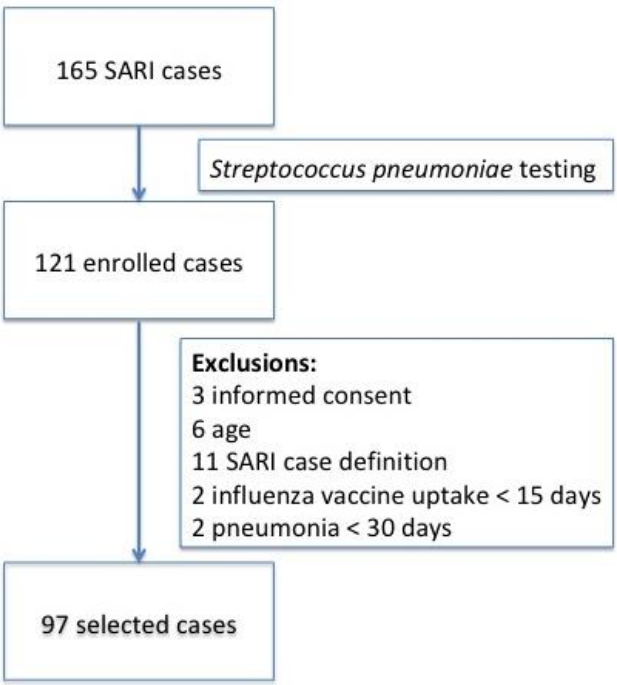

Figure 1. Case selection algorithm

Notes: SARI: severe acute respiratory infection.

Final sample comprised 97 SARI cases and Table 2 presents the description of selected cases.

Table 2. SARI and pneumococcal pneumonia cases characteristics

	SARI (n=97) % (IC95%)	Strept (+) 10,3 % SARI n/N	PP 5,7 % SARI n/N
Age (years), mean	80.8 (79.3-82.2)	77.8	77.6
65-79 years	38.1 (28.9-48.3)	7/10	3/5
≥80 years	61.9 (51.7-71.1)	3/10	2/5
Sex, male	35.1 (26.1-45.2)	4/10	2/5
Smoking	29.5 (21.1-39.6)	5/10	3/5
Antibiotics	17.7 (11.2-26.8)	2/10	0/5
Chest radiography	39.3 (29.6-50.0)	5/10	5/5
≥ 2 chronic conditions	80.4 (71.3-87.2)	6/10	5/5
Respiratory tuberculosis	10.7 (5.8-19.0)	1/10	0/5
Influenza	52.6 (42.5-62.5)	5/10	2/5
Seasonal influenza vaccine (2017/18)	44.7 (35.0-55.0)	2/10	0/5
PPSV23	3.5 (1.1-10.3)	0/10	0/5
PCV13	4.7 (1.7-12.1)	1/10	1/5

Notes: SARI: severe acute respiratory infection; Strept(+): SARI cases that had a positive urinary antigenic test; PP: pneumococcal pneumonia; PPSV23: pneumococcal polysaccharide vaccine; PCV13: 13-valent pneumococcal conjugated vaccine

From the 97 SARI cases, 10 (10.3 %) had a positive test for *Streptococcus pneumoniae* (urine antigenic test or hemoculture) and of those 5 (5.7 % of selected SARI cases) had also a chest radiography compatible with pneumonia.

Both pneumococcal vaccines were less frequent than season influenza vaccine in SARI cases.

The proportion of SARI cases that had a positive test for *Streptococcus pneumonia* increased among those with chest radiography compatible with pneumonia (14.3%).

Forty nine urine specimens were sent to the National Reference Laboratory for *S. pneumoniae* for urinary antigen testing, three of which were positive. These three positive specimens were sent to RIVM for additional serotyping and all were positive for serotypes 3 and 20.

Regarding to missing information (Table 3), almost all of collected variables had less than 5 % of missing values, except pneumococcal vaccination data.

Table 3. Missing data in each collected variable

Variable	n (%)
Age	0 (0)
Sex	0 (0)
≥ 2 chronic conditions	0 (0)
Smoking	2 (2.1)
Antibiotics	1 (1.0)
Pneumonia	3 (3.1)
Chest radiography	8 (8.2)
History of personal pulmonary tuberculosis	4 (4.1)
Influenza	0 (0)
Seasonal influenza vaccine (2017/18)	1 (1.0)
PPSV23	9 (9.3)
PCV13	12 (12.4)
Date of seasonal influenza vaccine uptake	4 (9.3)*
Date of PPSV23 uptake	1 (30.0)**
Date of PCV13 uptake	0 (0)

* considering the 43 cases vaccinated with seasonal influenza vaccine; ** considering the 3 cases vaccinated with PPSV23

Notes: PPSV23: pneumococcal polysaccharide vaccine; PCV13: 13-valent pneumococcal conjugated vaccine

4 Discussion

The achieved participation rate (72.2%) indicates a high compliance of health professionals and patients to collect additional data and samples for this branch of the study. This high acceptance of the study by the health professionals might be linked to the importance to better characterize elderly SARI patients. In addition, the low resources needed to collect additional data for the study might contributed to the high participation rate.

The quality of collected data is generally good, as the proportion of missing data were below 5% for most of the variables. Information regarding to variables newly included in the questionnaire in 2017/18 season, as having chest radiography compatible with pneumonia, was more prone to be missed. This might indicate that the questions were not enough clear or that an additional effort should be performed during the validation process. PPSV23 and PCV13 vaccination data, namely date of vaccine uptake, were the variable with higher number of missing values. This is due the inexistence of a universal vaccination registry until 2018 and the higher difficult to get accurate information from patient or his relatives when compared to seasonal influenza vaccine uptake. However, given that a universal vaccination registry is under implementation in Portugal, this limitation will be over passed in next few years.

However, the number of PP cases reached along the season was low and probably underestimate the number of hospitalized PP cases in elderly in 2017/18 season. As SARI cases invited to participate in EVA hospital represented 46.8 % of all potential selected SARI cases (2), we cannot exclude that a selection bias occurred during the SARI selection process if uninvited cases were those who were more prone to have a bacterial infection accordingly to the presented clinical presentation.

Considering the growing need to assess the overall impact of influenza vaccine it seems necessary to estimate the influenza vaccine effectiveness against frequent influenza complications, namely bacterial pneumonia. In settings where there is no conditions to put in place different studies protocols for cases selection, we considered the SARI case definition is appropriate for influenza and bacterial pneumonia cases selection as the clinical presentation and data needed to collect can be similar and its differential diagnostic part of the individual case management. Thus, it seems plausible that increasing the participation rate in EVA Hospital might contribute to increase the proportion of PP among SARI cases. The efficacy of case selection could be improved if having a chest radiography compatible with pneumonia was added as inclusion criterion for *Streptococcus pneumoniae* testing.

In this context, testing systematically SARI for influenza and for *Streptococcus pneumoniae* might contribute to increase knowledge regarding SARI aetiology, allowing identify risk factors for bacterial pneumonia following influenza.

PP cases selected among participating EVA hospital patients were added to the sample of PP considering to estimate IVE against PP using the screening method.

5 References

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4. Horita N, Miyazawa N, Kojima R, Kimura N, Inque M, Ishigatsubo Y, Kaneko T. Sensitivity and specificity of the Streptococcus pneumonia urinary antigen test for unconcentrated urine from adult patients with pneumonia: A meta-analysis. Respirology 2013; 18: 1177–83.

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ANNEX 2: Data Dictionary (3 pages)

Variable name	Type	Values and coding	Definition
HOSP	String		Hospital Centre
ID	Numeric (count)	Id	Unique number for patient
AGE	Numeric (count)	integer	Age (years)
AGE_GROUP	Numeric (categoric)	1 = <65 years 2 = 65-79 years 3 = ≥80 years	
SEX	Numeric (binary)	0 = female 1 = male	Sex of study participant
ADMISSION	Date	dd/mm/yyyy	Date of admisson
SEASON	Numeric (categoric)	1 = 2013/14 2 = 2014/15 3 = 2015/16 4 = 2016/17 5 = 2017/18	Influenza season
INST	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Institutionalized
PNEUMO	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Positive result for *St. pneumoniae*
AG	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Urinary antigenic test
HC	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Hemoculture
SP	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Sputum test
LBA	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Bronchoalveolar lavage
ISCHEMIC	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Ischemic heart disease
HTA	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	High blood pressure
CI	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Cardiac insufficiency
DIABETES	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Diabetes

CRD	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Chronic respiratory disease includes: asthma, chronic bronchitis, emphysema, bronchopulmonary dysplasia, cystic fibrosis, pneumoconiosis and pulmonary fibrosis
IMUNO	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Immunodeficiency congenital or acquired: conditions that suppress the immune function due to underlying disease and/or therapy, e.g. chemotherapy, HIV infection
CANCER	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Cancer
OTHER_CO	String		Other underlying condition
OBESITY	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Obesity
CD	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	2 or more chronic conditions
SMOK	Numeric (binary)	0 = No 1 = Yes (smoker and former smoker) 9 = unknown/missing	Tobacco use
ALC	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Alcohol abuse
FLUVAC	Numeric (binary)	0 = No 1 = Yes (≥15 days) 2 = Yes (<15 days) 9 = unknown/missing	Received seasonal influenza vaccine in current season
FLUVAC_DATE	Date	dd/mm/yyyy 9 = unknown/missing	Uptake date
PCV13	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Received PVC 13
PCV13_ DATE	Date	dd/mm/yyyy	PCV13 uptake date

		9 = unknown/missing	
PPSV23	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Received PPSV23
PPSV23_ DATE	Date	dd/mm/yyyy 9 = unknown/missing	PPSV23 uptake date
OUT	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Occurred out of influenza seasson
NOSOCOMIAL	Numeric (binary)	0 = No 1 = Yes 9 = unknown/missing	Nosocomial pneumonia