

# Estimating the burden of hospitalization for pneumococcal pneumonia in a general population aged 50 years or older and implications for vaccination strategies

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**Abbreviations:** PCV, pneumococcal conjugate vaccine; PPV, polysaccharide pneumococcal vaccine; HDR, hospital discharge records; ICD-9 CM, International Classification of Disease, Ninth Revision, Clinical Modification; PP1, pneumococcal pneumonia; PP2, fraction of unspecified bacterial pneumonia due to *S. pneumoniae*; PP3, fraction of unspecified pneumonia due to *S. pneumoniae*; SP, specified pneumonia; UP, unspecified pneumonia; SBP, bacterial pneumonia due to specified agents; UBP, bacterial pneumonia due to unspecified agents

*Streptococcus pneumoniae* is a major cause of human infectious diseases worldwide. Despite this documented evidence, data on pneumococcal disease rates among general populations are scant because of the frequent lack of cultural identification. In this study we propose a model for estimating the burden of pneumococcal pneumonia on hospitalizations.

The study was performed by analyzing administrative and clinical data of patients aged 50 years or older, resident in Sicily, and hospitalized, from 2005 to 2012. Demographic information, admission/discharge dates, discharge status, and up to 6 discharge diagnoses coded according to ICD-9 CM were collected for each hospitalized patient.

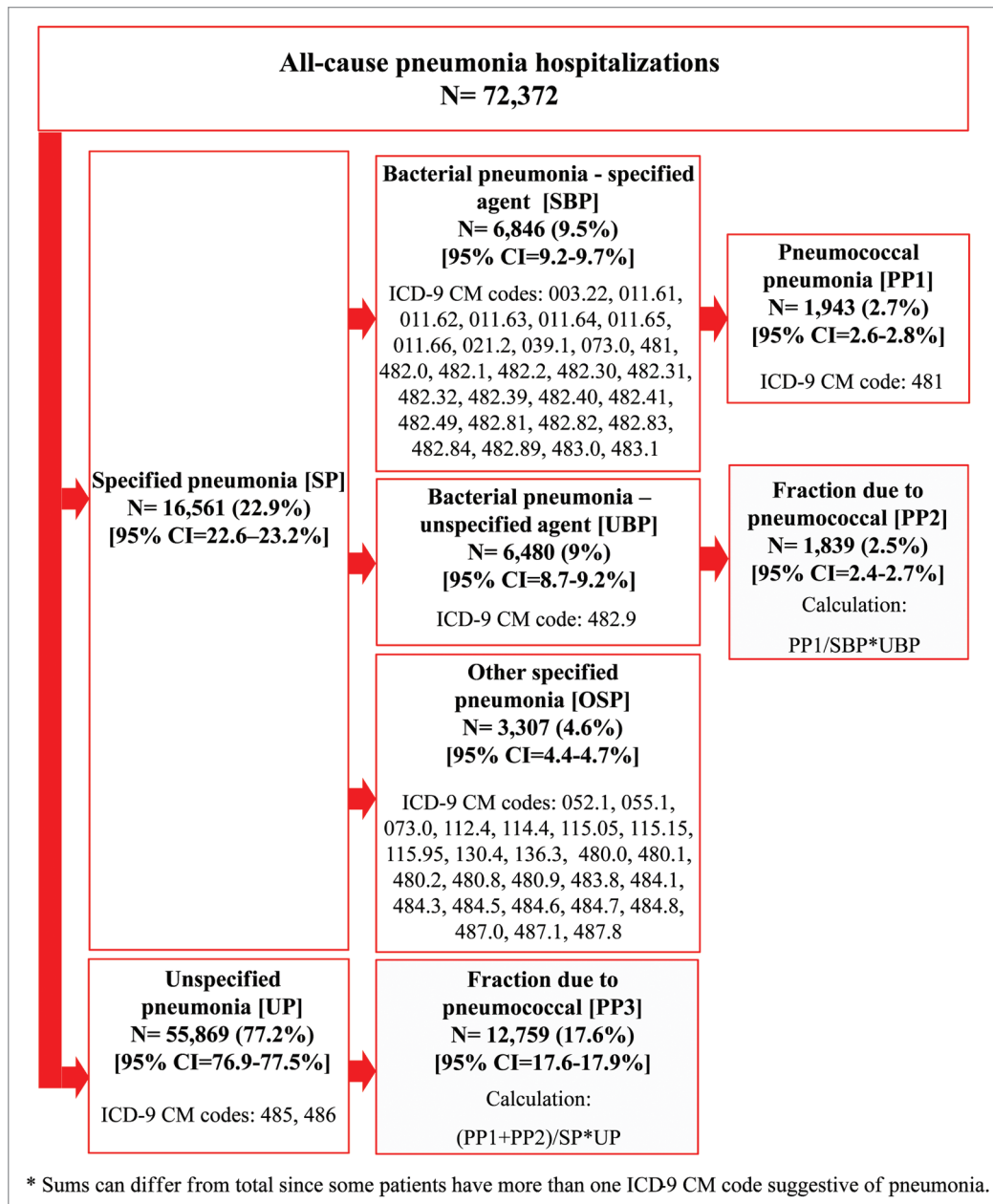
During the 8-year study period, a total of 72 372 hospitalizations with at least one ICD-9 CM diagnosis code suggestive of all-cause pneumonia were recorded. Of these, 1943 (2.7%) hospitalizations had specific ICD-9 CM diagnosis codes for pneumococcal pneumonia. According to the proposed model, 16 541 (22.9%) pneumonia out of all-cause pneumonia was estimated to be attributable to *S. pneumoniae*. Pneumococcal pneumonia and model-estimated pneumococcal pneumonia had mean hospitalization rates of 13.4 and 113.3/100 000, respectively, with a decreasing temporal trend. The risk of hospitalization for pneumococcal pneumonia was strongly correlated with age ( $P < 0.001$ ). Our model provides data usable to construct suitable decisional models for the decision-makers and could allow to the responsables of healthcare facilities to assess the budget impact if they hypothesize to offer vaccination for pneumococcal disease to certain cohorts of subjects aged 50 years or older. In our area, the high estimated hospitalization rates among adults aged  $\geq 65$  years suggest the need to implement effective preventive strategies (e.g., vaccination) tailored for these groups.

## Introduction

*Streptococcus pneumoniae* is a major cause of invasive (bacteremic pneumonia, meningitis, and septicemia) and non-invasive (non bacteremic pneumonia and otitis media) human infectious diseases, with high worldwide annual rates of morbidity and mortality, particularly in children and the elderly.<sup>1,2</sup> The incidence, prevalence, and mortality due to pneumococcal diseases vary widely, both in different countries and over time, likely in relation to improved knowledge and management of the related diseases, and principally to the implementation of universal vaccination campaigns on a national basis.<sup>3</sup>

In fact, vaccination remains the only public health strategy that, by reducing the incidence of the pneumococcal diseases, plays a major role in decreasing the global burden.<sup>4</sup> Two types of vaccines are currently available worldwide: a pneumococcal conjugate vaccine (PCV), initially recommended for infant immunization, and a pure polysaccharide pneumococcal vaccine (PPV), recommended for adult immunization. Several international health authorities, including the Region of Sicily's Health Commission, have recommended pneumococcal vaccination in both children and older adults as the best strategy for reducing the circulation of *S. pneumoniae* in these populations.<sup>5</sup>

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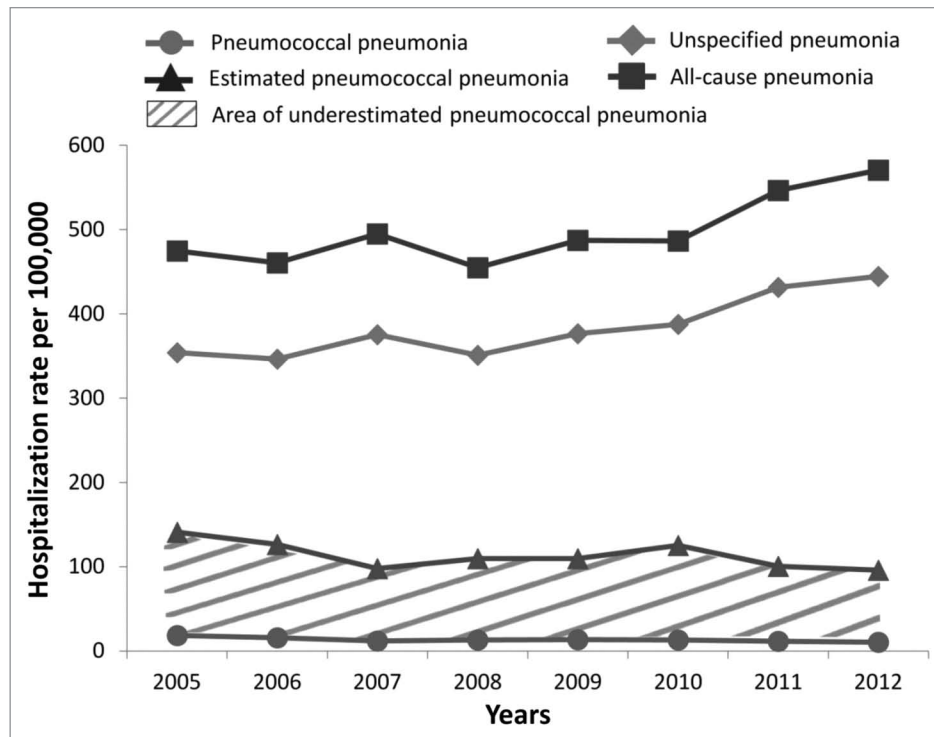
**Figure 1.** ICD-9 CM codes for all-cause pneumonia recorded, as principal or secondary diagnosis, in a total of 72 372 hospitalizations for pneumonia in Sicilian patients (white boxes), and calculated fractions for estimating specific pneumococcal pneumonia cases (grey boxes).

Following these recommendations, in Sicily PCV vaccination for children was introduced in the regional immunization program and actively offered from 2005, with very high coverage, resulting in a significant reduction in pneumococcal disease.<sup>6,7</sup>

PPV has been also recommended for adults aged >65 y and persons who have certain underlying medical conditions that may increase the risk of pneumococcal infection.<sup>8</sup> However, despite these recommendations, PPV coverage in Sicily is currently extremely low among adults.

Furthermore, data on the burden of pneumococcal diseases are scant due to the frequent lack of cultural identification of the causal agent during the medical care of the disease. As a consequence, the etiologic fraction attributable to *S. pneumoniae* may be underestimated or, alternatively, overestimated, considering all potentially attributable pneumococcal diseases in the absence of microbiological identification.

In this study we propose the application of a model for estimating the burden of pneumococcal pneumonia on hospitalizations of patients aged 50 y or older and resident in Sicily.



**Figure 2.** Hospitalization rate trends of all-cause pneumonia, unspecified pneumonia, pneumococcal pneumonia, and model estimated pneumococcal pneumonia (the striped area indicates pneumococcal pneumonia cases estimated by the model).

## Results

During the 8-y study period, a total of 72372 hospitalizations with at least one ICD-9 CM diagnosis code suggestive of all-cause pneumonia were reported in Sicily among adults aged  $\geq 50$  y. **Figure 1** shows the ICD-9 CM diagnosis codes for total episodes of hospitalizations for pneumococcal pneumonia in Sicilian patients.

Overall, 1943 (2.7%; 95% CI = 2.6–2.8%) hospitalizations had specific ICD-9 CM diagnosis codes for pneumococcal pneumonia. Pneumococcal pneumonia patients had a mean age of  $73.3 \pm 11.3$  y and 60% ( $n = 1165$ ) were male. The median length of in hospital stay was 9 d (interquartile range = 7).

In the same period, 6480 and 55869 hospitalizations included ICD-9 CM codes for unspecified bacteria or unspecified cause, accounting for 9% (95% CI = 8.7–9.2%) and 77.2% (95% CI = 76.9–77.5%) out of all-cause pneumonia, respectively. According to the proposed model, 1839 (28.4%; 95% CI = 27.3–29.5%) of the 6480 unspecified bacterial pneumonia and 12759 (22.8%; 95% CI = 22.5–23.2%) of the 55869 unspecified pneumonia were estimated to be attributable to *S. pneumoniae*, accounting for a total of 16541 (22.9%; 95% CI = 22.6–23.1%) hospitalizations.

**Figure 2** depicts hospitalization rate trends of all-cause pneumonia, unspecified pneumonia, pneumococcal pneumonia and model-estimated pneumococcal pneumonia. All-cause pneumonia and unspecified pneumonia increased over time, with mean incidence rates of 497 and 383.4 cases/100000, respectively. Otherwise, pneumococcal pneumonia and model-estimated pneumococcal pneumonia had mean hospitalization

rates of 13.4 and 113.3/100000, respectively, with a decreasing temporal trend (chi-square test for trend = 42.8 and 124.1, respectively;  $P$  value  $< 0.001$  in both cases).

Incidence rates of unspecified bacterial pneumonia and bacterial pneumonia (mean incidence rates of 44.5 and 47 cases/100000, respectively) were relatively constant over time (data not shown).

**Table 1** shows hospitalization rates estimated for pneumococcal pneumonia by age and year of hospital admission. Annual hospitalization rates for pneumococcal pneumonia ranged from 141.1 cases per 100000 in 2005 (95% CI = 137.4 to 148.8) to 95.9 cases per 100000 in 2012 (95% CI = 91.5 to 100.4).

The risk of hospitalization for pneumococcal pneumonia was found to be strictly correlated with age ( $P < 0.001$  by chi-square test for trend in all years), increasing about 15-fold from age class 50–54 y to  $\geq 80$ .

## Discussion

In Italy there are no reliable sources of information on invasive pneumococcal pneumonia incidence since these infections are not included in the national notification system.<sup>9</sup> Hospital discharge databases, therefore, are the only source for a timely and inexpensive picture of the epidemiology of almost all severe diseases, as they provide a complete record of all hospitalizations, and include standardized diagnosis code lists that enable secular trend analysis of incident disease for a given population.

**Table 1.** Estimated hospitalization rates (cases per 100 000 Adults) for pneumococcal pneumonia in Sicily (2005 through 2012)

	2005	2006	2007	2008	2009	2010	2011	2012
<b>Age group</b>								
<b>50–54</b>	34.0	28.5	21.5	34.8	21.0	27.0	25.3	28.3
<b>55–59</b>	43.6	37.9	38.9	47.5	51.5	35.8	21.9	23.6
<b>60–64</b>	75.9	53.7	48.6	66.6	58.9	48.9	43.8	23.2
<b>65–69</b>	89.2	93.1	59.2	59.8	59.3	77.4	56.0	66.5
<b>70–74</b>	125.8	122.1	93.1	95.0	122.1	138.5	93.3	52.1
<b>75–79</b>	252.3	219.0	184.7	224.8	161.8	210.4	215.8	178.2
<b>80 or more</b>	509.7	475.2	344.2	306.9	397.4	451.4	349.2	395.7
<b>Total</b>	141.1	126.3	97.9	109.5	109.7	125.3	100.6	95.9

Despite these advantages, hospital discharge databases are subject to some limitations that are common to all passive surveillance systems, such as under-diagnosis or deficiencies in reporting. For infectious diseases, these problems are at least in part due to the frequent empirical clinical management of the diseases without an etiologic identification of the causative agent, which in Italy has been estimated to occur in more than two-thirds of the hospitalizations for pneumonia.<sup>10</sup>

In view of this, several studies have reported that ICD-9 CM codes suggestive of pneumococcal pneumonia have good specificity, but poor sensitivity.<sup>11,12</sup> Very low sensitivity can be hypothesized in our area, as in others, considering that hospitalization for pneumococcal pneumonia represents less than 3% of all-cause pneumonia, whereas previous studies performed in several European nations, including Italy, have reported that *S. pneumoniae* is usually implicated in 11.9% to 68.3% of adult community-acquired pneumonia.<sup>10</sup>

In order to control for underreporting, we designed a model that estimates a burden of hospitalizations for pneumococcal pneumonia in an age group that, during the study period, in Sicily has accounted for a large proportion of the general population, increasing from 34.6% in 2005 to 38% in 2012.

The model shows estimated morbidity rates more than 8-fold higher than that observed by analyzing specific ICD-9 CM codes. These estimates seem to be realistic for 2 reasons.

First, annual hospitalization rates estimated in Sicily for pneumococcal pneumonia are included in the same size range as that calculated in other Italian areas, where they ranged from 62.9 cases per 100 000 persons aged 65–74 y to 422.7 per 100 000 aged  $\geq 85$ .<sup>13</sup>

Second, these estimates allow us to calculate that ICD-9 CM codes suggestive of pneumococcal pneumonia would have a sensitivity of 11.7%, which is similar to, but conservatively higher than, the 8% observed in other Italian studies.<sup>14</sup> Both these values underline that up to 90% of pneumococcal pneumonia cases may remain undetected, and are also consistent with the finding that in Italy the causative agent of community-acquired pneumonia is isolated only in a small fraction (<35%) of hospitalization cases.<sup>10</sup>

Nonetheless, further studies are necessary to confirm the validity of the proposed model.

Irrespective of the validity of the assumptions underlying the model, our study also found that the hospitalization rates for pneumococcal pneumonia increase in our age strata, and are more than 15-fold higher in older patients, with a decreasing temporal trend in all age groups from 2005 through 2012.

The higher risk with age is a well known and documented phenomenon that has been attributed to immunosenescence and the increasing frequency of co-morbidities in the elderly, suggesting that the policy strategies for implementing vaccination in adults by age could differ by geographic area according to local demography and epidemiology.<sup>15–17</sup> Notably, our data indicate that though pneumococcal pneumonia has been diagnosed in all age groups, vaccinating persons  $\geq 65$  may be the most cost-effectiveness public health strategy in our setting.

We also found a slight, though constant, reduction of pneumococcal pneumonia cases over time. Several studies have found that adults may benefit from extensive childhood pneumococcal vaccination through indirect effects.<sup>18</sup> In our region, the childhood conjugate vaccination for pneumococcal was introduced in the regional immunization program and actively offered from 2005, with rapidly increasing vaccination coverage, so the observed decline among adult populations could be attributed to the indirect, or herd, protection provided by pneumococcal conjugate vaccines in childhood.<sup>6,19</sup> On the other hand, a residual role may also be played by the small fraction of adults vaccinated with PPV23 vaccine.

Consonant with our findings, a study found an annual reduction in hospitalization for pneumonia among adults in the United States in the decade after the introduction of PCV7 in the infant immunization schedule.<sup>20</sup> In our study, all-cause pneumonia hospitalizations did not decrease over time. Though we are not able to elucidate possible determinants for this different trend, it can be hypothesized that several behavioral and normative factors and confounders (e.g., prevalence of smokers in the general population, influenza and influenza vaccination coverage, hospital admission thresholds) may be responsible for this difference in findings.

It should be noted that our study was not designed specifically to assess the impact of the current preventive measures and, in this sense, the impossibility of controlling for the previously

cited and other potential confounding factors may well be a major limitation of our study, as well as other retrospective studies. Finally, our model should be considered conservative for invasive pneumococcal diseases because it overlooks other invasive sites different from pneumonia and, including only hospitalized cases of pneumococcal pneumonia, enabled us to estimate severe cases, excluding information on mild cases treated in out-patient settings.

Despite these limitations, our model provides data usable to construct suitable decisional models for the decision-makers and could allow to the responsables of healthcare facilities to assess the budget impact if they hypothesize to offer vaccination for pneumococcal disease to certain cohorts of subjects aged 50 y or older. In our area, the relatively high estimated hospitalization rates among adults aged  $\geq 65$  y highlight the need to enhance active surveillance, and implement effective preventive strategies (e.g., vaccination) tailored for these age groups.

## Material and Methods

This study evaluated the administrative and clinical data of patients resident in Sicily, a large Italian region of about 5000000 residents. All data included in the analyses were obtained by the Region of Sicily's Health Commission, which routinely collects hospital discharge records (HDR) from all of the region's hospitals. The Regional Hospital Discharge Database, which was established in 1994, collects complete data on hospitalizations from both public and private hospitals. Each HDR includes demographic information (birthplace, residence, gender, and date of birth), admission and discharge dates, discharge status (categorized as "discharged/transferred" or "expired"), and up to 6 discharge diagnoses (1 principal and 5 secondary diagnoses) coded according to International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9 CM).

All patients aged 50 y or older and hospitalized in acute-care hospitals from 2005 to 2012 with at least one ICD-9 CM code among those reported in **Figure 1**, either as principal or secondary diagnosis, were used for estimating hospitalization rates due to pneumococcal pneumonia.

Hospitalization of Sicilian residents that occurred outside the region was also included in the analysis, while multiple hospitalizations due to transfers were combined. Admissions for transferred patients were followed until discharge or death.

The study was approved by the Institutional Review Board of the AOUP "P. Giaccone" of Palermo, Italy.

### Model design

As shown in **Figure 1**, considering that pneumococcal pneumonia (*PP1*;  $n = 1943$ ) represented 28.4% of bacterial pneumonia due to specified agents (*SBP*;  $n = 6846$ ), the same

percentage was expected to be attributable to pneumococcal among bacterial pneumonia due to unspecified agents (*UBP*;  $n = 6480$ ). Thus, the total number of unspecified bacterial pneumonia due to *S. pneumoniae* (*PP2*; estimated  $n = 1839$ ) was obtained with the following equation:

$$PP2 = \frac{PP1}{SBP} \times UBP \quad (1)$$

Since pneumococcal pneumonia (*PP1+PP2*;  $n = 3782$ ) accounted for 22.8% of all specified pneumonia (*SP*;  $n = 16561$ ), the same percentage was expected to be attributable to pneumococcal among all unspecified pneumonia (*UP*;  $n = 55869$ ). Thus, the fraction of unspecified pneumonia due to *S. pneumoniae* (*PP3*; estimated  $n = 12759$ ) was calculated with the following equation:

$$PP3 = \frac{(PP1 + PP2)}{SP} \times UP \quad (2)$$

Finally, the estimated hospitalized pneumococcal pneumonia was calculated as the sum of pneumococcal pneumonia (*PP1*) and the fractions of unspecified bacterial pneumonia and unspecified pneumonia due to *S. pneumoniae* (*PP2* and *PP3*, respectively).

### Statistical analysis

Absolute and relative frequencies with 95% confidence intervals (CI) were calculated for qualitative variables, while quantitative variables were summarized as mean  $\pm$  standard deviation when normally distributed or otherwise as median (interquartile range). Data normality was verified by the Shapiro–Wilk test for normality. The data trends were evaluated by using the chi-square test for trends.

Annual total and age-specific hospitalization rates (5-y strata) (2005–2012) were calculated by dividing the annual number of hospitalizations for the resident Sicilian population aged over 49 y on the 1st of the following year (data obtained from ISTAT).<sup>21</sup> Rates are expressed as hospitalized pneumococcal pneumonia/100000 per year, with a 95% CI. A two-tailed *P* value of  $<0.05$  was considered statistically significant. All data were analyzed with the R statistical software package.

### Ethical approval

The study was approved by the Institutional Review Board of the AOUP "P. Giaccone" of Palermo, Italy.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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