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Effectiveness of the 13-valent pneumococcal conjugate vaccine against adult pneumonia in Italy: a case-control study in a two-year prospective cohort

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Abstract

Objectives Current strategies to prevent adult pneumococcal disease have been recently reviewed in Italy. We did a post-licensure study to assess the direct effectiveness (VE) of the 13-valent pneumococcal conjugate vaccine (PCV13) against adult pneumococcal community-acquired pneumonia (pCAP).

Study design Between 2013-2015, a two-year prospective cohort study of adults with CAP was conducted in the Apulia region of Italy where the average vaccine uptake of PCV13 was 32% among adults ≥65 years. The test-negative design was used to assess VE against all episodes of confirmed pCAP and vaccine-type (VT) CAP. VE in a subgroup of patients managed in the community was also measured using a matched case-control design. VE was calculated as one minus the OR times 100%.

Results The overall VE of PCV13 was 33.3% (95% CI -93.1% to 77.0%) against pCAP irrespective of serotype and 54.2% (95% CI -210.2% to 93.2%) against VT-CAP in the cohort of adults ≥65 years. The VE was 71.4% (95% CI -379.8% to 98.3%) against VT-CAP in the age groups at higher vaccine uptake. For the subgroup of cases managed in the community, the overall VE against disease due to any pneumococcal strain was 88.1% (95% CI 4.2% to 98.5%) and was 91.7% (95% CI 13.1% to 99.2%) when we controlled for underlying conditions.

Conclusions PCV13 appears effective against all confirmed pCAP already with modest levels of uptake in the population of adults ≥65 years of age. Additional studies are needed to confirm these direct vaccine benefits.

Keywords PCV13, Pneumococcal conjugate vaccine, Vaccine effectiveness, Adult, Italy, Community-acquired pneumonia

Strengths and limitation of this study

- This is the first study to investigate the direct effectiveness of PCV13 for prevention of adult pneumococcal community-acquired pneumonia requiring hospitalization or managed in the community.
- We have been able to estimate PCV13 VE already with modest levels of vaccine uptake in the target population.
- The active surveillance of CAP was performed in a single regional setting leading to a small study size reducing the power to detect statistically significant effects.
- The test-negative method may have overestimated PCV13 VE if, by reducing the risk of acquiring vaccine-type serotypes, vaccination increases the risk of acquiring non vaccine-type serotypes as is likely to be the case if there is serotype replacement.

INTRODUCTION

Pneumonia is the fourth-leading cause of death globally and *Streptococcus pneumoniae* is by far the most frequent pathogen recovered from patients with community-acquired pneumonia (CAP), accounting for 12 to 85% of all CAP cases.[1-5] Children younger than five years of age, the elderly and people with certain underlying diseases are at an increased risk of developing a more severe course of pneumococcal CAP (pCAP) as well as complications, including death.[2,4]

Routine administration of the 7-valent conjugate vaccine (PCV7) since 2000 and of the second-generation conjugate vaccines (PCV10 and PCV13) since 2010 has resulted in an overall reduction in the rates of pneumococcal disease in both vaccinated and unvaccinated children, and indirectly among adults in several countries, owing to herd immunity.[6-7] However, the most recent available data suggest that significant burden still results from pneumococcal infection in older adults despite the impact of childhood PCV vaccination.

In the United States, the annual incidence of community-acquired pneumonia requiring hospitalization in 2010-2012 was 24.8 cases (95% CI 23.5 to 26.1) per 10,000 adults 18 years of age or older, with a prevalence of pneumococcal disease of 5% and an incidence that was almost 5 times as high among adults 65 years of age or older as among younger adults.[8] In 2013, an estimated 10% of CAP cases in adults aged ≥65 years were caused by *S. pneumoniae* serotypes potentially preventable with the use of PCV13 in this population.[9] On August 13, 2014, the Advisory Committee on Immunization Practices (ACIP) recommended routine use of PCV13 among adults aged ≥65 years in series with the currently recommended 23-valent pneumococcal polysaccharide vaccine (PPSV23 - administered at least one year later).[9]

In the UK, incidence of adult pneumococcal pneumonia declined over the 2008-2013 period, with serotypes included in PCV13 declining post-PCV13 introduction, suggesting an early herd protection effect from infant PCV13 on adult bacteraemic and non-bacteraemic disease.[10] Despite this, the most recent available data from 2012-2013 showed an incidence of 20.6 per 100,000 population for hospitalized adult pneumococcal CAP and 8.6 per 100,000 population for PCV13 serotype CAP.[10] PCV13 is not currently part of the UK adult vaccination programme while PPV23 continues to be offered to those aged 65 years and over and the indicated risk groups.[11]

In Italy, high infant PCV13 coverage has been achieved since 2011 (vaccine uptake rate 90-95%).[12] For adults, only PPSV23 was recommended for routine immunization of those aged ≥65 years and at-risk individuals, but the vaccine uptake rates have been low to date. In recent years, some Italian regions have recommended PCV13 to adults with underlying diseases and to the elderly (immunization of one or more age cohorts ≥65 years).[13]

Impact of PCV infant vaccination on adult pneumococcal pneumonia has not been well established in Italy. As a matter of fact, the hospitalization rates for pneumococcal pneumonia in the elderly population have remained relatively stable over the past decade, indicating a lack of herd protection amongst older age groups.[14] Factors influencing this trend are controversial.[15] However, because the incidence of CAP remains strongly age dependent,[16] the impact of a continually ageing population in Italy and the higher immunologic risk in elderly people (the so-called immunosenescence) on CAP incidence in the future requires close observation and continued efforts to determine the most effective adult pneumococcal vaccination strategy.[1, 17]

In 2014, the results of the Community-Acquired Pneumonia Immunization Trial in Adults (CAPITA) conducted in The Netherlands demonstrated 45.6% (95% CI 21.8% to 62.5%) efficacy of PCV13 against a first episode of vaccine-type pneumococcal pneumonia, 45.0% (95% CI 14.2% to 65.3%) efficacy against a first episode of vaccine-type non-bacteremic and noninvasive pneumococcal pneumonia, and 75.0% (95% CI 41.4% to 90.8%) efficacy against a first episode of vaccine-type invasive disease among adults aged ≥65 years.[18]

Evidence from the CAPITA trial led to the ACIP recommendations,[9, 19-20] of which a review is planned for 2018 owing to potential changes in the epidemiological situation. In particular, studies evaluating the post-licensure effectiveness of PCV13 for prevention of invasive and non-bacteremic pneumococcal pneumonia among adults ≥65 years old using a case control design are needed.[20] This study addresses this unmet need.

We report findings of the direct impact of PCV13 from a two-year prospective study of a cohort of pneumococcal CAP adults.

Methods

From January 2013 until January 2015, a prospective, multicenter, population-based, active surveillance study of adults with CAP was conducted over two years in Apulia, a large Italian region of approximately 4,000,000 inhabitants. PPSV23 was introduced in Apulia in 2000 for use in adults aged ≥65 years and was replaced by PCV13 in November 2011 for adults aged 65, 70, and ≥75 years.[21] In 2015, the average vaccine uptake of PCV13 was 32% amongst adults aged 65-75 years (11 cohorts) and 10% in the overall population >75 years.[22]

According to 2013 census figures, the designated surveillance area included about 788,000 adults 65 years of age or older.[23] Patients were enrolled in two different study settings from a network of 31 sentinel physicians. Surveillance for suspected CAP was conducted by 16 treating physicians among patients presenting at 13 hospitals located in the region (a total of 13,841 patients admitted to Departments of Respiratory Medicine in 2013-2014) and by 15 general practitioners (GPs) providing primary care for a total of 5,010 persons aged ≥65 years throughout the region.

Adults ≥65 years with symptoms suggestive of lower respiratory tract infection were eligible for enrolment if they presented to a study hospital or to their GP for a clinical assessment; resided in the study region; had at least two of the following clinical criteria: new cough or sputum production, fever >38.0°C or hypothermia <36.1°C, chest pain, dyspnea, tachypnea, new altered mental status, abnormal lung examination, respiratory failure, leukocytosis (>10 x10^9 white blood cells/liter or >15% bands) or leukopenia (<4.5 x10^9 white blood cells/liter), C-reactive protein value >3 times the upper limit of normal, hypoxemia with a partial oxygen pressure <60 mm Hg while the patient was breathing room air; and had evidence of new infiltrates on chest radiography consistent with pneumonia.[24] Exclusion criteria were discharge from hospital within the preceding 10 days and residence in a nursing home, long-term care facility, or other institution.

Written informed consent was obtained from all the patients or their caregivers before enrolment. Study sentinel physicians used a standardised electronic Case Report Form to collect information regarding patient demographics, clinical information, microbiological investigations and status regarding receipt of pneumococcal vaccination; pneumonia severity was assessed using the CURB-65 score (Confusion, Urea >7 mmol/L, Respiratory rate ≥30 breaths/min, low systolic <90 mm Hg or diastolic ≤60 mm Hg Blood pressure,

age ≥65 years). Patients were contacted 30 days after enrolment for outcome measures collection (30-day mortality, recovery with *sequelae*).

The study protocol was approved by the Institutional Review Board at the Apulian Regional Observatory for Epidemiology (PROT:18/OER/2012 February 20, 2012). The study was conducted according to the principles expressed in the Declaration of Helsinki.

Blood samples and nasopharyngeal swabs were obtained from the patients who presented to sentinel centers/GPs with symptoms of lower respiratory tract infection within 24 hours after presentation. In the case of patients with a productive cough, sputum was obtained. Bronchoalveolar-lavage (BAL) samples, blood-culture and sputum specimens that had been obtained for clinical care were sent to the Regional Reference Laboratory for Invasive Bacterial Diseases and analysed for the study.

S. pneumoniae was isolated by PCR and multiplex sequential PCR. Bacterial genomic DNA was extracted from 200 µl of biological samples using the QIAamp Dneasy Blood and Tissue kit (Qiagen), according to the manufacturer's instructions. Detection of *S. pneumoniae* was performed using a commercial multiplex assay (Pneumobacter ACE Detection for blood and Meningitis ACE Detection for CSF, Seegene; Sensitivity: detection limit of the Seeplex Pneumobacter Ace Detection = 10 copy/reaction − 10 copy/3 µl DNA). *S. pneumoniae* serotyping was performed on PCR positive samples through a sequential multiplex PCR.[25] Twenty-nine primer pairs were designed to target serotypes 1, 3, 4, 5, 6 A/B, 7F, 7C, 8, 9V, 10A, 11A, 12F, 14, 15A, 15 B/C, 16F, 17F, 18, 19A, 19F, 20, 22F, 23F, 31, 33F, 34, 35B, 35F, and 38. A primer pair (primers cpsA-f and cpsA-r) was also included as an internal control targeting the cpsA (pneumococcal capsular polysaccharide synthesis gene) locus found in all pneumococci.[26] The amplified products, ranging from 250 bp to 988 bp, were analyzed by means of electrophoresis on a 2% agarose gel (Life Technologies) and visualization under UV light.

Patients with a positive PCR result for *S. pneumoniae* on blood/sputum/BAL were deemed to have pneumococcal CAP. Nasopharyngeal swabs samples were not used for the diagnosis of pCAP, due to the poor sensitivity and specificity previously reported.[8]

Vaccine Effectiveness analysis

To estimate the vaccine effectiveness (VE) of PCV13 in the prevention of pneumococcal CAP, a test-negative design was performed on cases enrolled during the study surveillance period. The analysis included two primary end points:

I. **VE in preventing confirmed pneumococcal CAP irrespective of serotype**, where cases were patients who had an episode of invasive or non-invasive pCAP due to any pneumococcal strain and controls were participants with an episode of non pneumococcal pneumonia;

II. **VE in preventing confirmed vaccine-type (VT) CAP**, where cases were patients with an episode of invasive or non-invasive pCAP due to vaccine-type strains and controls were patients with non–vaccine-type (NVT) pneumococcal CAP.

These two end points were further assessed among patients who had underlying conditions.

The exposure of interest was vaccination with PCV13. The exposure to PPSV23 given <5 years prior to study enrolment was also assessed. Data were based on verified vaccine information and not self-report.

To further study the effectiveness of PCV13 in the prevention of episodes of confirmed pCAP managed in the community, a subgroup analysis of cases reported by GPs network was performed. This analysis was performed according to a 1:3 matched case-control design. For every enrolled patient, a list of potential asymptomatic controls was generated from GPs subjects' medical records. Three controls, matched by GP, age, and gender, were selected at random for each case. Controls were enrolled if they provided written informed consent to their GP.

Statistical Analysis

Statistical analyses were performed in STATA (version 14; StataCorp, College Station, TX, USA).

Chi-square analysis or Fisher's exact test, 2-sided, were used to calculate the p-value for the difference between study groups in percentages of subjects reporting a pCAP or non pneumococcal pneumonia.

Logistic regression was used to calculate the unadjusted odds ratios (ORs) of vaccination together with 95% confidence intervals (95% CI). In the subgroup analysis, the matched ORs for vaccination in cases and

controls were calculated using conditional logistic regression, controlling for the presence of underlying conditions. Vaccine effectiveness was calculated as one minus the OR times 100%.

RESULTS

From the 1,867 eligible adults identified over the two-year period, 226 consented to the study. Of these, 176 (77.9%) were admitted to Departments of Respiratory Medicine and 50 (22.1%) were registered with a GP. Pneumonia severity was low, moderate and high in 47 (20.8%), 167 (73.9%) and 12 (5.3%) adults, respectively. Of 226 enrolled patients, 40 were excluded as they were unable to provide a blood or a sputum/BAL sample, leaving 186 in the cohort for analyses. The median age of the cohort was 79 years (interquartile range, 73 to 85) and 65 (34.9%) were female. Twenty (10.8%) had received PCV13 and 60 (32.3%) had received PPSV23 <5 years prior to enrolment (Table 1).

Table 1. Characteristics of adults with community-acquired pneumonia requiring hospitalization or managed in the community

	Pneumococcal group (N = 59)	Non-pneumococcal group (N = 127)	CAP cohort (N = 186)	P
Demographics				
Age years	79 (71 to 83)	79 (73 to 85)	79 (73 to 85)	
Male	42 (71.2)	79 (62.2)	121 (65.1)	0.232
Reporting				
Hospital physicians	38 (64.4)	105 (82.7)	143 (76.9)	Referent
GPs	21 (35.6)	22 (17.3)	43 (23.1)	0.0059
Any underlying comorbidity*				
Chronic heart disease	28 (47.5)	70 (55.1)	98 (52.7)	0.33
Chronic respiratory disease	29 (49.2)	52 (40.9)	81 (43.6)	0.293
Diabetes	14 (23.7)	32 (25.2)	46 (24.7)	0.829
Chronic kidney disease	2 (3.4)	9 (7.1)	11 (5.9)	0.32
Chronic liver disease	2 (3.4)	3 (2.4)	5 (2.6)	0.687
Malignancy	0	4 (3.1)	4 (2.1)	0.234
Asplenia	1 (1.7)	1 (0.8)	2 (1.1)	0.576
Status regarding receipt of pneumococcal vaccination†				
PCV13	5 (8.5)	15 (11.8)	20 (10.8)	0.452
PPSV23 given <5 years prior to study enrolment	20 (33.9)	40 (31.5)	60 (32.3)	0.853
Outcomes§				
30-day mortality	2 (3.4)	2 (1.6)	4 (2.2)	0.480
Recovery with *sequelae*	5 (8.5)	20 (15.7)	25 (13.4)	0.208

Data are number, median (interquartile range) or number (%). *The groups were not mutually exclusive and therefore do not sum to 100%. †For both vaccines, patients were considered to be vaccinated if they had received the vaccine at least 2 weeks before enrolment. Data were missing for four patients in the non-pneumococcal group. One patient had received a dose of PCV13 ≥1 year after receipt of a PPSV23 dose given <5 years prior to study enrolment. §Data were missing for 20 patients in the pneumococcal group and 40 patients in the non-pneumococcal group.

A nasopharyngeal swab was obtained from 171 of the 186 (91.9%) participants, a blood sample from 152 (81.7%), a sputum specimen from 139 (74.7%), and a BAL specimen from 3 (1.6%). *S. pneumoniae* was detected in 71 (41.5%) nasopharyngeal swab, 2 (1.3%) blood, 55 (39.6%) sputum, and 2 (66.7%) BAL.

Of 186 in the CAP cohort, 59 (31.7%, 95% CI 25.7 to 38.9%) adults were identified as pneumococcal CAP. More than half (31, 52.5%) had disease caused by one of the PCV7 serotypes, of which 23F, 9V, 14, 4 and 19F were the most common; 8 (13.6%) had CAP due to additional PCV13 serotypes, of which 19A and 3 were the most common; 9 (15.2%) had CAP due to serotypes only contained in PPSV23; 4 (6.8%) had non-vaccine-type disease; 7 (11.9%) had nontypeable pneumococcal CAP (Figure 1). Five had received one dose of PCV13 and 20 one dose of PPSV23 <5 years prior to enrolment. Of 39 patients infected with serotypes contained in PCV13, three had received this vaccine (disease caused by 9V in two cases and 23F in one) (Figure 1).

Baseline characteristics and outcomes were balanced between pneumococcal and non-pneumococcal groups (Table 1).

Vaccines Effectiveness

VE estimate was 33.3% (95% CI -93.1% to 77.0%) against pneumococcal CAP irrespective of serotype and 54.2% (95% CI -210.2% to 93.2%) against vaccine-type CAP in the cohort of adults ≥65 years. PCV13 VE was 71.4% (95% CI -379.8% to 98.3%) with respect to VT-CAP in the age group at higher vaccine uptake (65-75 years).

The VE was 34.8% (95% CI -90.6% to 77.7%) against CAP due to any pneumococcal strain and 61.3% (95% CI -172.2% to 94.5%) against CAP due to vaccine-type strains for adults with underlying conditions.

PCV13 VE against the two primary end points in patients naïve to PPSV23 or vaccinated with PPSV23 ≥5 years prior to enrolment was 27.5% (95% CI -117.9% to 75.9%) and 29% (95% CI -403.0% to 90.0%) respectively, lower than VE estimates in subgroups defined irrespective of PPSV23 immune status (Table 2).

Table 2. PCV13 effectiveness estimates against all episodes of confirmed pneumococcal CAP and CAP due to vaccine serotypes in adults by vaccination status and the presence of underlying conditions

	Cases vaccinated/ unvaccinated	Controls vaccinated/ unvaccinated	Vaccine effectiveness	95% CI

Pneumococcal CAP (any strain)	5/54	15/108*	33.3%	-93.1% to 77.0%
Vaccine-type CAP	3/36	2/11†	54.2%	-210.2% to 93.2%
Vaccine-type CAP in the age group at higher vaccine uptake (65-75 years)	2/14	1/2†	71.4%	-379.8% to 98.3%
Pneumococcal CAP in patients with ≥1 comorbid disorder	5/46	15/90*	34.8%	-90.6% to 77.7%
Vaccine-type CAP in patients with ≥1 comorbid disorder	3/31	2/8†	61.3%	-172.2% to 94.5%
Pneumococcal CAP in patients naïve to PPSV23 or vaccinated with PPSV23 ≥5 years prior to enrolment	5/34	14/69*	27.5%	-117.9% to 75.9%
Vaccine-type CAP in patients naïve to PPSV23 or vaccinated with PPSV23 ≥5 years prior to enrolment	3/19	2/9†	29.0%	-403.0% to 90.0%

*Controls were patients with an episode of non pneumococcal pneumonia. †Controls were patients with NVT pneumococcal CAP.

PPSV23 was not shown to have effectiveness against pneumococcal CAP in either all adults (VE -4.1%, 95% CI -104.9% to 47.2%) or those with comorbidities (VE -5.6%, 95 %CI: -117.4% to 48.8%) naïve to PCV13.

Subgroup analysis of 21 confirmed cases reported by GPs network (Table 1) provided evidence of effectiveness of PCV13 in preventing pneumococcal CAP managed in the community.

We identified 4,965 asymptomatic adults as potential controls, of whom 129 (2.6%) died and 95 (1,9%) were excluded because they left the GP's practice during the study period. Among the remaining 4,741 controls, 63 (three per case) were selected for the analysis.

Review of GP records showed that the controls were of similar age and gender to cases, but differed in other characteristics. One case (4.8%) and one control (1.6%) had received PCV13 at least 2 weeks before enrolment, whereas 18 controls (28.6%) were vaccinated during the study period. Sixteen cases (76.2%) and 36 controls (57.1%) had at least one comorbid disorder.

The overall effectiveness of PCV13 against disease due to any pneumococcal strain was 88.1% (95% CI 4.2% to 98.5%) and was 91.7% (95% CI 13.1% to 99.2%) when we controlled for underlying conditions (Figure 2).

DISCUSSION

To our knowledge, this is the first study to investigate the effectiveness of PCV13 for prevention of invasive and non-invasive pneumococcal pneumonia among adults. Moreover, we estimated the vaccine effectiveness against confirmed pneumococcal CAP managed in the community, where most patients are treated as outpatients. Given that a substantial proportion of studies are based on hospitalised patients, the true burden of disease is not known in Europe, where only Finland, Spain and the UK have precise epidemiological data on CAP.[27-28]

Although several studies have reported a decline in the incidence of pneumococcal disease in adults following implementation of infant PCVs,[6-7] we identified no real-world studies evaluating the direct impact of an adult PCV13 vaccination programme. In this study, PCV13 serotypes accounted for 66% of all confirmed pneumococcal CAP. National Invasive Bacterial Diseases surveillance data from Italy showed that, despite an uncertain reduction in the proportion of PCV13 serotypes in the period 2010–2012, these were still responsible for about 56% of cases among over-65s.[15] These data suggest that PCV13 vaccine-type pneumococcal disease continues to have a high burden in adults in Italy despite childhood PCV13 vaccination and would indicate a lack of herd protection effects in older age groups, in comparison to the vaccinated paediatric population.[14-15, 29] The most recent data in the UK suggest that, despite an ongoing trend of reduced incidence of PCV13 serotype CAP from paediatric conjugate vaccines,[10, 30] PCV13 serotypes currently account for 12.6% of all cases of CAP and 41% of pneumococcal CAP in adults.[27] Adults aged ≥65 years may have therefore a great potential for disease reduction from PCV13 and may be a primary target of vaccination programmes.[18] This is particularly noteworthy for Italian population because the burden of CAP and pneumococcal disease in general is expected to increase with the aging society, even with the impact of childhood and adult vaccine programmes.[27, 31]

Moreover, in our study, most of CAP was caused by PCV13 serotypes 23F, 9V, 14, 19A, 4, 19F, and 3 (Figure 1) that are among the less susceptible to antibiotics.[32] Recent findings for Switzerland showed that, while non-susceptible serotypes 19A, 9V, 6B, 23F and 14 among invasive and non-invasive *S. pneumoniae* decreased over time in patients up to age 64 years vaccination due to PCVs infant

vaccination,[33-35] in patients older than 64 years with invasive *S. pneumoniae* resistance rates remained unchanged.[36] By preventing disease caused by resistant strains, adult PCV13 vaccination provides a robust strategy for combating antimicrobial resistance that is a growing problem in Europe.[37]

On January 19, 2017, PCV13 has been introduced into the routine vaccination schedule in Italy for all adults 65 years of age followed by a dose of PPV23.[38] The decision-making regarding its introduction was based on the CAPITA trial results and the ACIP recommendations, but also on a long history of experience of adult pneumococcal conjugate vaccination in some Italian regions including Apulia.[13, 21]

In this prospective cohort study of adults with CAP we found that PCV13 was protective against all episodes of confirmed pneumococcal CAP (VE 33.3%) and against disease caused by serotypes contained in the vaccine (VE 54.2%). Recently published findings of the exploratory efficacy endpoint analysis of the CAPITA trial showed VE of 29% for all episodes of confirmed pneumococcal CAP and 43% for all non-bacteremic and noninvasive episodes of VT pneumococcal CAP,[39] findings consistent with the primary efficacy analysis.[18]

Moreover, our results showed that PCV13 was effective for prevention of vaccine-type CAP already with modest levels of uptake in the target population (VE 71.4%). These data would suggest that rapid uptake and improved coverage of PCV13 among adults in the short term could maximize its impact.[20, 40]

The incidence of pneumococcal CAP is greatly increased in many individual clinical risk groups.[41] Since when the ACIP recommended PCV13 for immunocompromised adults in 2012, there remains little evidence regarding the efficacy of the vaccine in at risk populations.[11, 18, 42] Our findings would suggest that vaccination with PCV13 is effective in preventing pneumococcal disease in adults ≥65 years with comorbid disorders. This observation, taken together with no effectiveness showed by PPV23 in our cohort, will require further studies to verify how adults with chronic diseases may fully benefit of the ACIP and the new Italian recommendations for the use of both PCV13 and PPSV23 in series. A recent systematic review and meta-analysis designed to estimate the efficacy of PPV23 in the prevention of pCAP, particularly in patients above 60 years of age and adults with underlying diseases, showed that PPV23 vaccination “alone” does not

demonstrate clear efficacy, supporting the administration of a dose of PCV13 first followed by a dose of PPV23 at least 8 weeks later.[2]

Another recent systematic review of the burden of vaccine preventable pneumococcal disease in UK adults did not identify studies that were conducted in the community, where the majority of pCAP is managed.[27] In our study, as it was designed to capture both invasive and non-invasive pneumococcal CAP, approximately 36% of cases had been reported by general practitioners, suggesting that hospital based studies may underestimate the true impact of pneumococcal disease. Subgroup analysis of cases managed in the community provided evidence that PCV13 had significant effectiveness with respect to CAP from any pneumococcal serotype and this value did not change when we controlled for the presence of underlying disorders.

This study has several limitations. First, it was performed in a single region with a long-lasting history of experience of adult pneumococcal conjugate vaccination. Therefore, data from our setting may not be representative of the entire Italian adult population or generalizable to other settings. Moreover, data regarding the epidemiology of pCAP in adults in Italy are very limited and a large variability among published studies exists.[15]

Second, the study size was small reducing the power to detect statistically significant effects, although pneumococcal aetiology was identified in 31.7% CAP adults. Recent corresponding figure from Rodrigo et al. for UK was 29.3%.[10] The main limitation, however, pertains to the small numbers of PCV13 vaccinated cases and controls underlying the estimation of the vaccine effectiveness accounting for wide 95% CIs including zero. Although VE estimates should be interpreted with caution, our calculation reflected the still low PCV13 coverage achieved in the vaccinated cohorts. It was, therefore, too early to narrow the confidence limits around the point-estimate of effectiveness.

Third, the test-negative method may overestimate VE if, by reducing the risk of acquiring VT serotypes, vaccination increases the risk of acquiring NVT as is likely to be the case if there is serotype replacement.

Fourth, we were not able to assess the effectiveness of individual vaccine serotypes, as there were too few cases to allow statistical comparison between study groups.

Nonetheless, our study pointed out important gaps regarding the burden of pneumococcal CAP in Italy where there are limited data outside of national surveillance of IPD and the only available data for non-invasive disease are limited to hospitalization for pneumococcal pneumonia that, however, lack of serotyping information.[15] The active surveillance of adult confirmed CAP, drawn from a relative stable population over a two-year period, was a strength of our study and allowed us to assess the effectiveness of the 13-valent pneumococcal conjugate vaccine against all confirmed CAP, without regard to serotype, the presence of underlying conditions, and the site of patient management (hospital/community).

Our results have clinical practice implications for pneumococcal vaccination policies in adults in countries where PCV13 is becoming part of routine immunization of the elderly. Additional studies are needed to confirm the direct vaccine benefits using surveillance and case-control designs.

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COMPETING INTERESTS

We have read and understood BMJ policy on declaration of interests and declare the following interests: RP reports grants from Pfizer, during the conduct of the study; grants, personal fees and non-financial support from Pfizer, personal fees and non-financial support from SanofiPasteurMSD, personal fees and non-financial support from GSK, outside the submitted work. DM reports grants and non-financial support from GSK, non-financial support from SanofiPasteurMSD, non-financial support from Pfizer, outside the submitted work. FF, MGC and MC declare that they have no competing interests.

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CONTRIBUTORS

RP and DM conceptualised and designed the work, analysed and interpreted data, and writing the manuscript. FF and MGC contributed to the data collection, managed the database and provided statistical support. MC performed the laboratory work. All authors have read and approved the final manuscript.

DATA SHARING STATEMENT

There are no unpublished data available.

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Figure 1. Number of cases of pneumococcal CAP by serotype and vaccination status (N=59)

Figure 2. PCV13 effectiveness (%) estimates against CAP due to any pneumococcal strain managed in the community*

* Fourteen cases (66.7%) had CAP caused by one of the PCV7 serotypes, of which 14 and 9V were the most common; three cases (14.3%) were due to additional PCV13 serotype 19A; three cases (14.3%) had CAP due to other serotypes; one (4.7%) had nontypeable pneumococcal CAP. One case vaccinated with PCV13 was caused by serotype 12F.

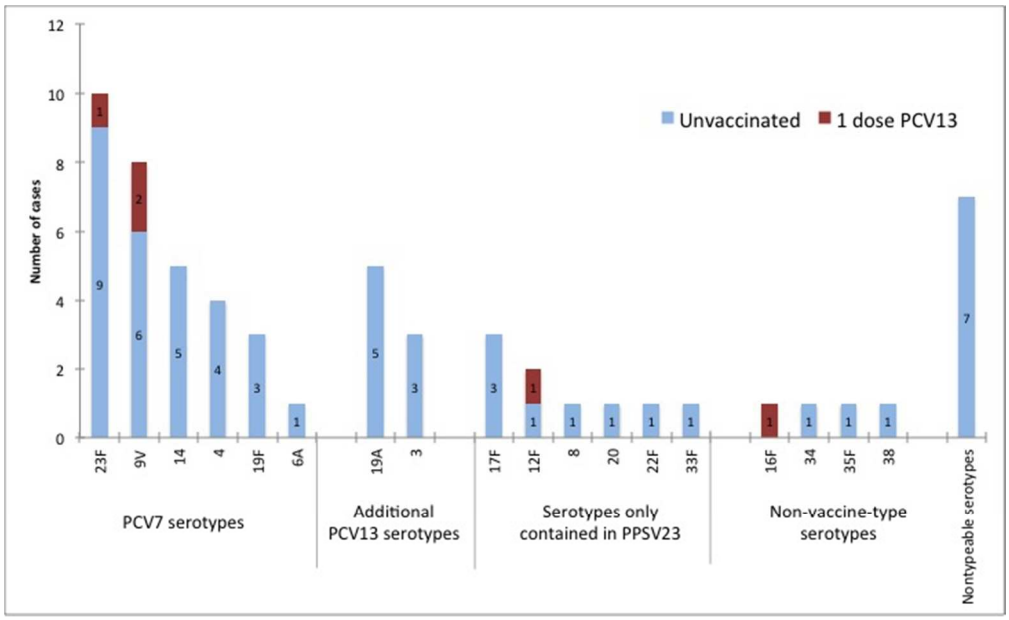

Figure 1. Number of cases of pneumococcal CAP by serotype and vaccination status (N=59)

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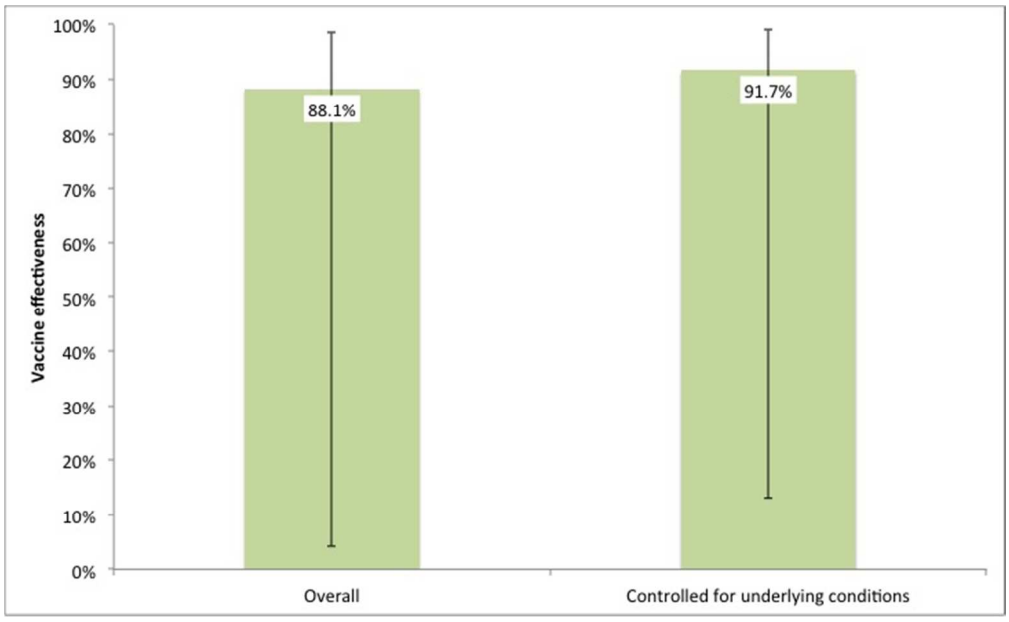

Figure 2. PCV13 effectiveness (%) estimates against CAP due to any pneumococcal strain managed in the community*

* Fourteen cases (66.7%) had CAP caused by one of the PCV7 serotypes, of which 14 and 9V were the most common; three cases (14.3%) were due to additional PCV13 serotype 19A; three cases (14.3%) had CAP due to other serotypes; one (4.7%) had nontypeable pneumococcal CAP. One case vaccinated with PCV13 was caused by serotype 12F.

256x156mm (72 x 72 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) If applicable, explain how loss to follow-up was addressed	8-9
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Effectiveness of the 13-valent pneumococcal conjugate vaccine against adult pneumonia in Italy: a case-control study in a two-year prospective cohort

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Effectiveness of the 13-valent pneumococcal conjugate vaccine against adult pneumonia in Italy: a case-control study in a two-year prospective cohort

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Abstract

Objectives Current strategies to prevent adult pneumococcal disease have been recently reviewed in Italy. We did a post-licensure study to estimate the direct effectiveness (VE) of the 13-valent pneumococcal conjugate vaccine (PCV13) against adult pneumococcal community-acquired pneumonia (pCAP).

Study design Between 2013-2015, a two-year prospective cohort study of adults with CAP was conducted in the Apulia region of Italy where the average vaccine uptake of PCV13 was 32% among adults ≥65 years. The test-negative design was used to estimate VE against all episodes of confirmed pCAP and vaccine-type (VT) CAP. VE in a subgroup of patients managed in the community was also estimated using a matched case-control design. VE was calculated as one minus the OR times 100%.

Results The overall VE of PCV13 was 33.2% (95% CI -106.6% to 82%) against pCAP irrespective of serotype and 38.1% (95% CI -131.9% to 89%) against VT-CAP in the cohort of adults ≥65 years. The VE was 42.3% (95% CI -244.1% to 94.7%) against VT-CAP in the age group at higher vaccine uptake. For the subgroup of cases managed in the community, the overall VE against disease due to any pneumococcal strain was 88.1% (95% CI 4.2% to 98.5%) and 91.7% (95% CI 13.1% to 99.2%) when we controlled for underlying conditions.

Conclusions Although our results are non-significant, PCV13 promises to be effective against all confirmed pCAP already with modest levels of uptake in the population of adults ≥65 years of age. Larger studies are needed to confirm the direct vaccine benefits.

Keywords PCV13, Pneumococcal conjugate vaccine, Vaccine effectiveness, Adult, Italy, Community-acquired pneumonia

Strengths and limitation of this study

- The test-negative method used in this study has reduced the risk for selection bias since both cases and controls were recruited in one process and arose from the whole population when the same enrolment criteria were met.
- The study was designed to capture CAP cases managed in the community, reducing the underestimate of the true impact of pneumococcal disease.
- The active surveillance of CAP was performed in a single regional setting leading to a small study size reducing the power to detect statistically significant effects.
- The test-negative method may have overestimated PCV13 VE if, by reducing the risk of acquiring vaccine-type serotypes, vaccination increases the risk of acquiring non vaccine-type serotypes as is likely to be the case if there is serotype replacement.

INTRODUCTION

Routine administration of the 7-valent conjugate vaccine (PCV7) since 2000 and of the second-generation conjugate vaccines (PCV10 and PCV13) since 2010 has resulted in an overall reduction in the rates of pneumococcal disease in both vaccinated and unvaccinated children, and indirectly among adults in several countries, owing to herd immunity.[1-2] However, the most recent available data suggest that significant burden still results from pneumococcal infection in older adults.

In the United States, the annual incidence of community-acquired pneumonia (CAP) requiring hospitalization in 2010-2012 was 24.8 cases (95% CI 23.5 to 26.1) per 10,000 adults 18 years of age or older, with a prevalence of pneumococcal disease of 5% and an incidence that was almost 5 times as high among adults 65 years of age or older as among younger adults.[3] In 2013, an estimated 10% of CAP cases in adults aged ≥65 years were caused by *S. pneumoniae* serotypes potentially preventable with the use of PCV13 in this population.[4]

In the UK, incidence of adult pneumococcal pneumonia declined over the 2008-2013 period, with serotypes included in PCV13 declining post-PCV13 introduction, suggesting an early herd protection effect from infant PCV13 on adult bacteraemic and non-bacteraemic disease. However, the most recent available data from 2012-2013 showed an incidence of 20.6 per 100,000 population for hospitalized adult pneumococcal CAP and 8.6 per 100,000 population for PCV13 serotype CAP.[5]

In Italy, high infant PCV13 coverage has been achieved since 2011 (vaccine uptake rate 90-95%).[6] For adults, only PPSV23 was recommended for routine immunization of those aged ≥65 years and at-risk individuals, but the vaccine uptake rates have been low to date. In recent years, some Italian regions have recommended PCV13 to adults with underlying diseases and to the elderly.[7]

Impact of PCV infant vaccination on adult pneumococcal pneumonia has not been well established in Italy. The hospitalization rates for pneumococcal pneumonia in the elderly population have remained relatively stable over the past decade, indicating a lack of herd protection amongst older age groups.[8]

In 2014, the CAPITA trial conducted in the Netherlands demonstrated the efficacy of PCV13 for the prevention, in those aged ≥65, of vaccine-type pneumococcal CAP.[9] Evidence from the CAPITA trial led to new ACIP PCV13 recommendations,[4, 10-11] of which a review is planned for 2018 owing to potential

changes in the epidemiological situation. In particular, studies evaluating the post-licensure effectiveness of PCV13 for prevention of invasive and non-bacteremic pneumococcal pneumonia among adults ≥65 years old using a case control design are needed.[11] This study attempts to address this unmet need.

We report findings of the direct impact of PCV13 from a two-year prospective study of a cohort of pneumococcal CAP adults.

Methods

From January 2013 until January 2015, a prospective, multicenter, population-based, active surveillance study of adults with CAP was conducted over two years in Apulia, a large Italian region of approximately 4,000,000 inhabitants. PPSV23 was introduced in Apulia in 2000 for use in adults aged ≥65 years and was replaced by PCV13 in November 2011 for adults aged 65, 70, and ≥75 years.[12] In 2015, the average vaccine uptake of PCV13 was 32% amongst adults aged 65-75 years (11 cohorts) and 10% in the overall population >75 years.[13]

According to 2013 census figures, the designated surveillance area included about 788,000 adults 65 years of age or older.[14] Patients were enrolled in two different study settings from a network of 31 sentinel physicians. Surveillance for suspected CAP was conducted by 16 treating physicians among patients presenting at 13 hospitals located in the region (a total of 13,841 patients aged ≥65 years admitted to Departments of Respiratory Medicine in 2013-2014) and by 15 general practitioners (GPs) providing primary care for a total of 5,010 persons aged ≥65 years throughout the region.

Adults ≥65 years with symptoms suggestive of lower respiratory tract infection were eligible for enrolment if they presented to a study hospital or to their GP for a clinical assessment; resided in the study region; had at least two of the eleven clinical criteria listed in Box 1; and had evidence of new infiltrates on chest radiography consistent with pneumonia.[15] Patients were excluded if they had been hospitalized recently (<10 days) or were functionally dependent nursing home, long-term care facility, or other institution residents (healthcare-associated pneumonia cases).

Box 1. Clinical criteria for definition of CAP

- New cough or sputum production
- Fever >38.0°C or hypothermia <36.1°C
- Chest pain
- Dyspnea
- Tachypnea
- New altered mental status
- Abnormal lung examination
- Respiratory failure
- Leukocytosis (>10 x109 white blood cells/liter or >15% bands) or leukopenia (<4.5 x109 white blood cells/liter)
- C-reactive protein value >3 times the upper limit of normal
- Hypoxemia with a partial oxygen pressure <60 mm Hg while the patient was breathing room air

Written informed consent was obtained from all the patients or their caregivers before enrolment. Study sentinel physicians used a standardised electronic Case Report Form to collect information regarding patient demographics, clinical information, microbiological investigations and status regarding receipt of pneumococcal vaccination; pneumonia severity was assessed using the CURB-65 score (Confusion, Urea >7 mmol/L, Respiratory rate ≥30 breaths/min, low systolic <90 mm Hg or diastolic ≤60 mm Hg Blood pressure, age ≥65 years). Patients were contacted 30 days after enrolment for outcome measures collection (30-day mortality, recovery with *sequelae*).

The study protocol was approved by the Institutional Review Board at the Apulian Regional Observatory for Epidemiology (PROT:18/OER/2012 February 20, 2012). The study was conducted according to the principles expressed in the Declaration of Helsinki.

Blood samples and nasopharyngeal swabs were obtained from the patients who presented to sentinel centers/GPs with symptoms of lower respiratory tract infection within 24 hours after presentation. In the case of patients with a productive cough, sputum was obtained. Bronchoalveolar-lavage (BAL) samples, blood-culture and sputum specimens that had been obtained for clinical care were sent to the Regional Reference Laboratory for Invasive Bacterial Diseases and analysed for the study.

S. pneumoniae was isolated by PCR and multiplex sequential PCR. Bacterial genomic DNA was extracted from 200 µl of biological samples using the QIAamp Dneasy Blood and Tissue kit (Qiagen), according to the manufacturer's instructions. Detection of *S. pneumoniae* was performed using a commercial multiplex assay (Pneumobacter ACE Detection for blood and Meningitis ACE Detection for CSF, Seegene; Sensitivity: detection limit of the Seeplex Pneumobacter Ace Detection = 10 copy/reaction − 10 copy/3 µl DNA). *S.*

pneumoniae serotyping was performed on PCR positive samples through a sequential multiplex PCR.[16] Twenty-nine primer pairs were designed to target serotypes 1, 3, 4, 5, 6 A/B, 7F, 7C, 8, 9V, 10A, 11A, 12F, 14, 15A, 15 B/C, 16F, 17F, 18, 19A, 19F, 20, 22F, 23F, 31, 33F, 34, 35B, 35F, and 38. A primer pair (primers cpsA-f and cpsA-r) was also included as an internal control targeting the cpsA (pneumococcal capsular polysaccharide synthesis gene) locus found in all pneumococci.[17] The amplified products, ranging from 250 bp to 988 bp, were analyzed by means of electrophoresis on a 2% agarose gel (Life Technologies) and visualization under UV light.

Patients with a positive PCR result for *S. pneumoniae* on blood/sputum/BAL were deemed to have pneumococcal CAP. Nasopharyngeal swabs samples were not used for the diagnosis of pCAP, due to the poor sensitivity and specificity previously reported.[3]

Vaccine Effectiveness analysis

To estimate the vaccine effectiveness (VE) of PCV13 in the prevention of pneumococcal CAP, a test-negative design was performed on cases enrolled during the study surveillance period. The analysis included two primary end points:

I. **VE in preventing confirmed pneumococcal CAP irrespective of serotype**, where cases were patients who had an episode of invasive or non-invasive pCAP due to any pneumococcal strain and controls were participants with an episode of non pneumococcal pneumonia;

II. **VE in preventing confirmed vaccine-type (VT) CAP**, where cases were patients with an episode of invasive or non-invasive pCAP due to vaccine-type strains and controls were patients with non-vaccine-type (NVT) pneumococcal CAP, non-typable isolates or non pneumococcal pneumonia.

These two end points were further assessed among patients who had underlying conditions.

The exposure of interest was vaccination with PCV13. The exposure to PPSV23 given <5 years prior to study enrolment was also assessed. Data were based on verified vaccine (both PCV13 and PPSV23) information and not self-report.

To further study the effectiveness of PCV13 in the prevention of episodes of confirmed pCAP managed in the community, post hoc analysis of a subgroup of cases reported by GPs network was performed. This

analysis was performed according to a 1:3 matched case-control design. For every enrolled patient, a list of potential asymptomatic controls was generated from GPs subjects' medical records. Three controls, matched by GP, age, and gender, were selected at random for each case. Controls were enrolled if they provided written informed consent to their GP. Study personnel contacted these GPs to obtain a medical and vaccination history for every control. Immunization information system was also used to verify vaccination histories.

Statistical Analysis

Statistical analyses were performed in STATA (version 14; StataCorp, College Station, TX, USA).

Chi-square analysis or Fisher's exact test, 2-sided, were used to calculate the p-value for the difference between study groups in percentages of subjects reporting a pCAP or non pneumococcal pneumonia.

Exact logistic regression was used to calculate the unadjusted odds ratios (ORs) of vaccination together with 95% confidence intervals (95% CI). In the post hoc subgroup analysis, the matched ORs for vaccination in cases and controls were calculated using conditional logistic regression, controlling for the presence of underlying conditions. Vaccine effectiveness was calculated as one minus the OR times 100%.

RESULTS

From the 1,867 eligible adults identified over the two-year period, 226 consented to the study. Main reasons why patients (or a relative) declined to participate were old age, difficulty in reading and/or understanding the invite letter, acute confusion or cognitive impairment, or a desire not to have medication altered. Of 226 patients recruited, 176 (77.9%) were admitted to Departments of Respiratory Medicine and 50 (22.1%) were registered with a GP. Pneumonia severity was low, moderate and high in 47 (20.8%), 167 (73.9%) and 12 (5.3%) adults, respectively. Forty patients were excluded as they were unable to provide a blood or a sputum/BAL sample, leaving 186 in the cohort for analyses. The median age of the cohort was 79 years (interquartile range, 73 to 85) and 65 (34.9%) were female. Twenty (10.8%) had received PCV13 and 60 (32.3%) had received PPSV23 <5 years prior to enrolment (Table 1). The seasonal distribution of CAP cases

followed a pattern similar to that of many other respiratory diseases, with similar peaks during the winter months of the two-year period (Figure 1).

Table 1. Characteristics of adults with community-acquired pneumonia requiring hospitalization or managed in the community

	Pneumococcal group (N = 59)	Non-pneumococcal group (N = 127)	CAP cohort (N = 186)
Demographics			
Age years	79 (71 to 83)	79 (73 to 85)	79 (73 to 85)
Male	42 (71.2)	79 (62.2)	121 (65.1)
Reporting			
Hospital physicians	38 (64.4)	105 (82.7)	143 (76.9)
GPs	21 (35.6)	22 (17.3)	43 (23.1)
Any underlying comorbidity*			
Chronic heart disease	28 (47.5)	70 (55.1)	98 (52.7)
Chronic respiratory disease	29 (49.2)	52 (40.9)	81 (43.6)
Diabetes	14 (23.7)	32 (25.2)	46 (24.7)
Chronic kidney disease	2 (3.4)	9 (7.1)	11 (5.9)
Chronic liver disease	2 (3.4)	3 (2.4)	5 (2.6)
Malignancy	0	4 (3.1)	4 (2.1)
Asplenia	1 (1.7)	1 (0.8)	2 (1.1)
Status regarding receipt of pneumococcal vaccination†			
PCV13	5 (8.5)	15 (11.8)	20 (10.8)
PPSV23 given <5 years prior to study enrolment	20 (33.9)	40 (31.5)	60 (32.3)
Outcomes§			
30-day mortality	2 (3.4)	2 (1.6)	4 (2.2)
Recovery with *sequelae*	5 (8.5)	20 (15.7)	25 (13.4)

Data are number, median (interquartile range) or number (%). *The groups were not mutually exclusive and therefore do not sum to 100%. †For both vaccines, patients were considered to be vaccinated if they had received the vaccine at least 2 weeks before enrolment. Data were missing for four patients in the non-pneumococcal group. One patient had received a dose of PCV13 ≥1 year after receipt of a PPSV23 dose given <5 years prior to study enrolment. §Data were missing for 20 patients in the pneumococcal group and 40 patients in the non-pneumococcal group.

A nasopharyngeal swab was obtained from 171 of the 186 (91.9%) participants, a blood sample from 152 (81.7%), a sputum specimen from 139 (74.7%), and a BAL specimen from 3 (1.6%). *S. pneumoniae* was detected in 71 (41.5%) nasopharyngeal swab, 2 (1.3%) blood, 55 (39.6%) sputum, and 2 (66.7%) BAL.

Of 186 in the CAP cohort, 59 (31.7%, 95% CI 25.7 to 38.9%) adults were identified as pneumococcal CAP. More than half (31, 52.5%) had disease caused by one of the PCV7 serotypes, of which 23F, 9V, 14, 4 and 19F were the most common; 8 (13.6%) had CAP due to additional PCV13 serotypes, of which 19A and 3 were the most common; 9 (15.2%) had CAP due to serotypes only contained in PPSV23; 4 (6.8%) had non-vaccine-type disease; 7 (11.9%) had nontypeable pneumococcal CAP (Figure 1). Five had received one dose

of PCV13 and 20 one dose of PPSV23 <5 years prior to enrolment. Of 39 patients infected with serotypes contained in PCV13, three had received this vaccine (disease caused by 9V in two cases and 23F in one) (Figure 2).

Baseline characteristics and outcomes were balanced between pneumococcal and non-pneumococcal groups (Table 1).

Vaccines Effectiveness

PCV13 VE estimate was 33.2% (95% CI -106.6% to 82%) against pneumococcal CAP irrespective of serotype and 38.1% (95% CI -131.9% to 89%) against vaccine-type CAP in the cohort of adults ≥65 years. The VE was 42.3% (95% CI -244.1% to 94.7%) with respect to VT-CAP in the age group at higher vaccine uptake (65-75 years).

The VE was 34.6% (95% CI -104.6% to 82.5%) against CAP due to any pneumococcal strain and 40.1% (95% CI -127.5% to 89.4%) against CAP due to vaccine-type strains for adults with underlying conditions.

PCV13 VE against the two primary end points in patients naïve to PPSV23 or vaccinated with PPSV23 ≥5 years prior to enrolment was 27.35% (95% CI -136.5% to 81.5%) and 17% (95% CI -234.7% to 85.9%) respectively, lower than VE estimates in subgroups defined irrespective of PPSV23 immune status (Table 2).

Table 2. PCV13 effectiveness estimates against all episodes of confirmed pneumococcal CAP and CAP due to vaccine serotypes in adults by vaccination status and the presence of underlying conditions

	Cases vaccinated/ unvaccinated	Controls vaccinated/ unvaccinated§	Vaccine effectiveness	95% CI
Pneumococcal CAP (any strain)	5/54	15/108*	33.2%	-106.6% to 82%
Vaccine-type CAP	3/36	17/126†	38.1%	-131.9% to 89%
Vaccine-type CAP in the age group at higher vaccine uptake (65-75 years)	2/14	8/32†	42.3%	-244.1% to 94.7%
Pneumococcal CAP in patients with ≥1 comorbid disorder	5/46	15/90*	34.6%	-104.6% to 82.5%
Vaccine-type CAP in patients with ≥1 comorbid disorder	3/31	17/105†	40.1%	-127.5% to 89.4%
Pneumococcal CAP in patients naïve to PPSV23 or vaccinated with PPSV23 ≥5 years prior to enrolment	5/34	14/69*	27.3%	-136.5% to 81.5%
Vaccine-type CAP in patients naïve to PPSV23 or vaccinated with PPSV23 ≥5 years prior to enrolment	3/19	16/84†	17%	-234.7% to 85.9%

*Controls were patients with an episode of non pneumococcal pneumonia. †Controls were patients with NVT pneumococcal CAP, non-typable isolates or non pneumococcal pneumonia. §Vaccine data were missing for four controls.

PPSV23 was not shown to have effectiveness against pneumococcal CAP in either all adults (VE -4%, 95% CI -115.4% to 50.4%) or those with comorbidities (VE -5.5%, 95 %CI: -130.5% to 52.2%) naïve to PCV13.

Post hoc subgroup analysis of 21 confirmed cases reported by GPs network (Table 1) provided estimates of PCV13 effectiveness in preventing pneumococcal CAP managed in the community.

We identified 4,965 asymptomatic adults as potential controls, of whom 129 (2.6%) died and 95 (1,9%) were excluded because they left the GP's practice during the study period. Among the remaining 4,741 controls, 63 (three per case) were selected for the analysis. Nine (14,2%) controls were replaced for difficulty in obtaining consent.

Review of GP records showed that the controls were of similar age and gender to cases, but differed in vaccination and clinical history: one case (4.8%) and one control (1.6%) had received PCV13 at least 2 weeks before enrolment, whereas 18 controls (28.6%) were vaccinated during the study period; 16 cases (76.2%) and 36 controls (57.1%) had at least one comorbid disorder.

The overall effectiveness of PCV13 against disease due to any pneumococcal strain was 88.1% (95% CI 4.2% to 98.5%) and 91.7% (95% CI 13.1% to 99.2%) when we controlled for underlying conditions (Figure 3).

DISCUSSION

To our knowledge, this is the first study to investigate the effectiveness of PCV13 for prevention of invasive and non-invasive pneumococcal pneumonia among adults ≥65 years. The overall VE was 33.2% against pCAP irrespective of serotype and 38.1% against VT-CAP. The VE was 42.3% against VT-CAP in the age group at higher vaccine uptake. Moreover, we estimated a vaccine effectiveness of 88.1% against confirmed pneumococcal CAP managed in the community, where most patients are treated as outpatients. Given that a substantial proportion of studies are based on hospitalised patients, the true burden of disease is not known in Europe, where only Finland, Spain and the UK have precise epidemiological data on CAP.[18-19]

In this study, PCV13 serotypes accounted for 66% of all confirmed pneumococcal CAP. National Invasive Bacterial Diseases surveillance data from Italy showed that, despite an uncertain reduction in the proportion of PCV13 serotypes in the period 2010–2012, these were still responsible for about 56% of cases among over-65s.[20] These data suggest that PCV13 vaccine-type pneumococcal disease continues to have a high burden in adults in Italy despite childhood PCV13 vaccination and would indicate a lack of herd protection effects in older age groups, in comparison to the vaccinated paediatric population.[8, 20-21] The most recent data in the UK suggest that, despite an ongoing trend of reduced incidence of PCV13 serotype CAP from paediatric conjugate vaccines,[5, 22] PCV13 serotypes currently account for 12.6% of all cases of CAP and 41% of pneumococcal CAP in adults.[18] In Ireland, in over 5 years following PCV13 introduction to routine childhood vaccination, the number of IPD associated with additional PCV13 serotypes in adults ≥65 years of age has remained relatively unchanged due to the persistence in serotypes 3 and 19A in this age-group.[23] In Spain, 13 years after introduction of PCV7/PCV13 for children, a significant proportion of adults continue to develop vaccine serotype CAP, suggesting an insufficient indirect protection. [24] Because it cannot be assumed that a decline in pneumococcal disease incidence observed in some countries will always be mirrored elsewhere in the same time, adults aged ≥65 years may have a great potential for disease reduction from PCV13 and may be a primary target of vaccination programmes.[9] This is particularly noteworthy for Italian population because the burden of CAP and pneumococcal disease in general is expected to increase with the aging society, even with the impact of childhood and adult vaccine programmes.[18, 25]

In our study, most of CAP was caused by PCV13 serotypes 23F, 9V, 14, 19A, 4, 19F, and 3 (Figure 2) that are among the less susceptible to antibiotics.[26] Recent findings for Switzerland showed that, while non-susceptible serotypes 19A, 9V, 6B, 23F and 14 among invasive and non-invasive *S. pneumoniae* decreased over time in patients up to age 64 years vaccination due to PCVs infant vaccination,[27-29] in patients older than 64 years with invasive *S. pneumoniae* resistance rates remained unchanged.[30] By preventing disease caused by resistant strains, adult PCV13 vaccination provides a robust strategy for combating antimicrobial resistance that is a growing problem in Europe.[31]

On January 19, 2017, PCV13 has been introduced into the routine vaccination schedule in Italy for all adults 65 years of age followed by a dose of PPV23.[32] The decision-making regarding its introduction was based on the CAPITA trial results and the ACIP recommendations, but also on a long history of experience of adult pneumococcal conjugate vaccination in some Italian regions including Apulia.[7, 12]

In this prospective cohort study of adults with CAP we found that PCV13 promise to be protective against all episodes of confirmed pneumococcal CAP (VE 33.2%) and against disease caused by serotypes contained in the vaccine (VE 38.1%). Recently published findings of the exploratory efficacy endpoint analysis of the CAPITA trial showed VE of 29% for all episodes of confirmed pneumococcal CAP and 43% for all non-bacteremic and noninvasive episodes of VT pneumococcal CAP,[33] findings consistent with the primary efficacy analysis.[9] On an ecological level, a preliminary analysis of hospitalization rates for adult pneumococcal CAP in Apulia region showed early PCV13 impact after the implementation of an adult vaccine programme (from 180,5 per 100,000 during 2006-2011 to 162,4 per 100,000 during 2012-2016; hospitalization risk ratio: 0,9 95% CI 0.83 to 0.97). [unpublished observations]

Moreover, our results showed that PCV13 promise to be effective for prevention of vaccine-type CAP already with modest levels of uptake in the target population (VE 42.3%). These data would suggest that rapid uptake and improved coverage of PCV13 among adults in the short term could maximize its impact.[11, 34]

The incidence of pneumococcal CAP is greatly increased in many individual clinical risk groups.[35] Since when the ACIP recommended PCV13 for immunocompromised adults in 2012, there remains little evidence regarding the efficacy of the vaccine in at risk populations.[36, 9, 37] Our findings would suggest that vaccination with PCV13 may be effective in preventing pneumococcal disease in adults ≥65 years with comorbid disorders. This observation, taken together with no effectiveness showed by PPV23 in our cohort, will require further studies to verify how adults with chronic diseases may fully benefit of the ACIP and the new Italian recommendations for the use of both PCV13 and PPSV23 in series. A recent systematic review and meta-analysis designed to estimate the efficacy of PPV23 in the prevention of pCAP, particularly in patients above 60 years of age and adults with underlying diseases, showed that PPV23 vaccination “alone”

does not demonstrate clear efficacy, supporting the administration of a dose of PCV13 first followed by a dose of PPV23 at least 8 weeks later.[38]

Another recent systematic review of the burden of vaccine preventable pneumococcal disease in UK adults did not identify studies that were conducted in the community, where the majority of pCAP is managed.[18] In our study, as it was designed to capture both invasive and non-invasive pneumococcal CAP, approximately 36% of cases had been reported by general practitioners, suggesting that hospital based studies may underestimate the true impact of pneumococcal disease. Post hoc subgroup analysis of cases managed in the community provided estimates of PCV13 effectiveness with respect to CAP from any pneumococcal serotype and this value did not change when we controlled for the presence of underlying disorders.

This study has several limitations. First, it was performed in a single region with a long-lasting history of experience of adult pneumococcal conjugate vaccination. Therefore, data from our setting may not be representative of the entire Italian adult population or generalizable to other settings. Moreover, data regarding the epidemiology of pCAP in adults in Italy are very limited and a large variability among published studies exists.[20]

Second, the recruitment rate was very low affecting the representativeness of the sample; however, there was not a risk for selection bias since both cases and controls were recruited in one process and arose from the whole population when the same enrolment criteria were met.

Third, 40 out of 226 enrolled patients were unable to provide a blood or a sputum/BAL sample, which could have led to underestimation or overestimation of pneumococcal aetiology rates. Owing to ethical and feasibility considerations, specimens were obtained only for clinical care and no invasive procedures were performed for this study, which may have reduced the microbiologic yield. However, 82% of the adults had at least one specimen type available for *S. pneumoniae* detection.

The study size was small reducing the power to detect statistically significant effects, although pneumococcal aetiology was identified in 31.7% CAP adults. Recent corresponding figure from Rodrigo et al. for UK was 29.3%.[5] The main limitation, however, pertains to the small numbers of PCV13 vaccinated cases and controls underlying the estimation of the vaccine effectiveness accounting for wide 95% CIs

including zero. Although VE estimates should be interpreted with caution, our calculation reflected the still low PCV13 coverage achieved in the vaccinated cohorts. It was, therefore, too early to narrow the confidence limits around the point-estimate of effectiveness.

Fourth, the test-negative method may overestimate VE if, by reducing the risk of acquiring VT serotypes, vaccination increases the risk of acquiring NVT as is likely to be the case if there is serotype replacement.

Fifth, we were not able to assess the effectiveness of individual vaccine serotypes, as there were too few cases to allow statistical comparison between study groups.

Nonetheless, our study pointed out important gaps regarding the burden of pneumococcal CAP in Italy where there are limited data outside of national surveillance of IPD and the only available data for non-invasive disease are limited to hospitalization for pneumococcal pneumonia that, however, lack of serotyping information.[20] The active surveillance of adult confirmed CAP, drawn from a relative stable population over a two-year period, was a strength of our study and allowed us to estimate the effectiveness of the 13-valent pneumococcal conjugate vaccine against all confirmed CAP, without regard to serotype, the presence of underlying conditions, and the site of patient management (hospital/community).

This study has clinical practice implications for pneumococcal vaccination policies in adults in countries where PCV13 is becoming part of routine immunization of the elderly. Although our results are non-significant, they can stimulate to perform larger studies that would probably confirm the vaccine effectiveness but probably with narrower confidence intervals than those presented here.

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COMPETING INTERESTS

We have read and understood BMJ policy on declaration of interests and declare the following interests: RP reports grants from Pfizer, during the conduct of the study; grants, personal fees and non-financial support from Pfizer, personal fees and non-financial support from SanofiPasteurMSD, personal fees and non-financial support from GSK, outside the submitted work. DM reports grants and non-financial support from GSK, non-financial support from SanofiPasteurMSD, non-financial support from Pfizer, outside the submitted work. FF, MGC and MC declare that they have no competing interests.

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CONTRIBUTORS

RP and DM conceptualised and designed the work, analysed and interpreted data, and writing the manuscript. FF and MGC contributed to the data collection, managed the database and provided statistical support. MC performed the laboratory work. All authors have read and approved the final manuscript.

DATA SHARING STATEMENT

There are no unpublished data available.

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Figure 1. Seasonal distribution of cases in the CAP cohort (N=186)

Figure 2. Number of cases of pneumococcal CAP by serotype and vaccination status (N=59)

Figure 3. PCV13 effectiveness (%) estimates against CAP due to any pneumococcal strain managed in the community*

* Fourteen cases (66.7%) had CAP caused by one of the PCV7 serotypes, of which 14 and 9V were the most common; three cases (14.3%) were due to additional PCV13 serotype 19A; three cases (14.3%) had CAP due to other serotypes; one (4.7%) had nontypeable pneumococcal CAP. One case vaccinated with PCV13 was caused by serotype 12F.

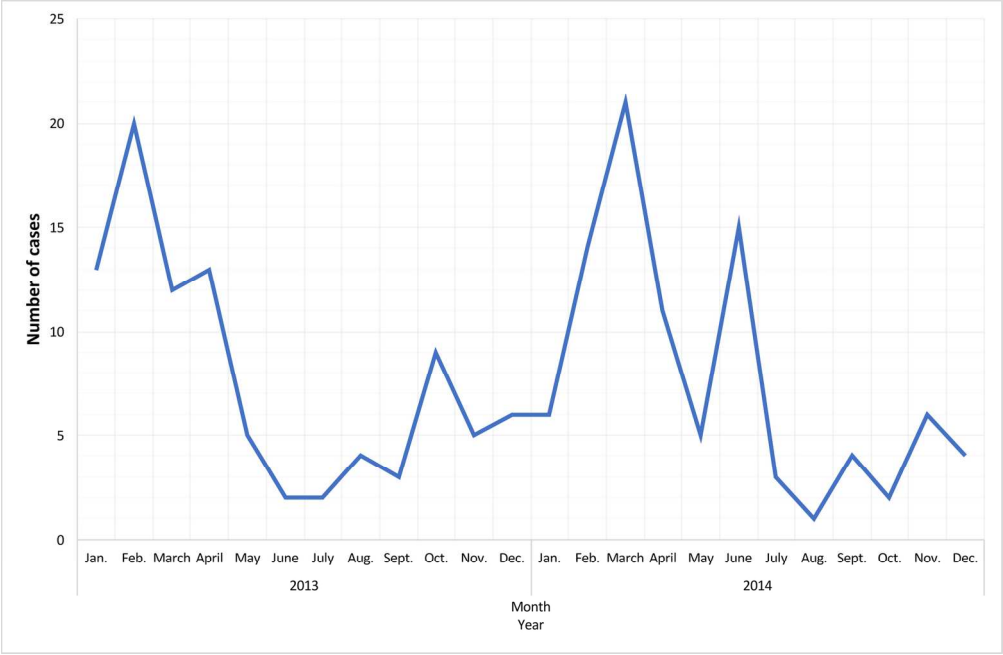

Figure 1. Seasonal distribution of cases in the CAP cohort (N=186)

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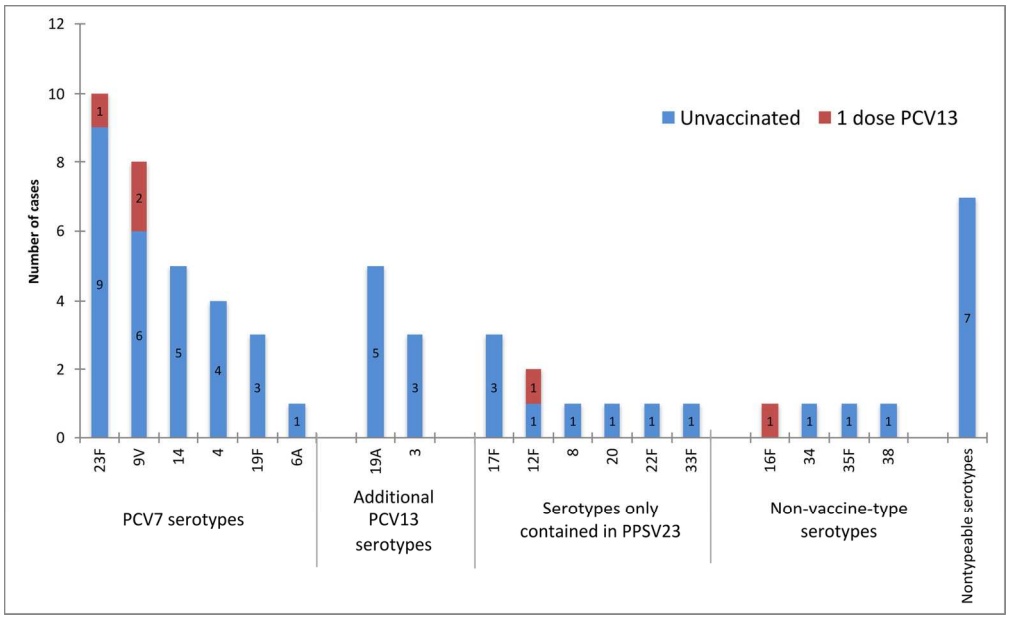

Figure 2. Number of cases of pneumococcal CAP by serotype and vaccination status (N=59)

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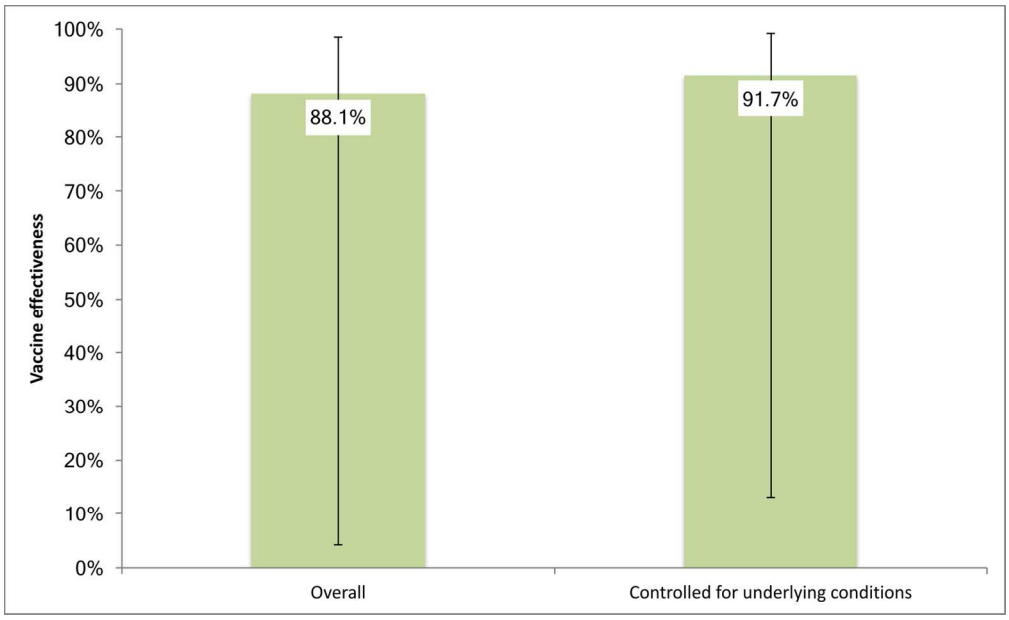

Figure 3. PCV13 effectiveness (%) estimates against CAP due to any pneumococcal strain managed in the community*

* Fourteen cases (66.7%) had CAP caused by one of the PCV7 serotypes, of which 14 and 9V were the most common; three cases (14.3%) were due to additional PCV13 serotype 19A; three cases (14.3%) had CAP due to other serotypes; one (4.7%) had nontypeable pneumococcal CAP. One case vaccinated with PCV13 was caused by serotype 12F.

156x95mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) If applicable, explain how loss to follow-up was addressed	8-9
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Effectiveness of the 13-valent pneumococcal conjugate vaccine against adult pneumonia in Italy: a case-control study in a two-year prospective cohort

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Effectiveness of the 13-valent pneumococcal conjugate vaccine against adult pneumonia in Italy: a case-control study in a two-year prospective cohort

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Abstract

Objectives Current strategies to prevent adult pneumococcal disease have been recently reviewed in Italy. We did a post-licensure study to estimate the direct effectiveness (VE) of the 13-valent pneumococcal conjugate vaccine (PCV13) against adult pneumococcal community-acquired pneumonia (pCAP).

Study design Between 2013-2015, a two-year prospective cohort study of adults with CAP was conducted in the Apulia region of Italy where the average vaccine uptake of PCV13 was 32% among adults ≥65 years. The test-negative design was used to estimate VE against all episodes of confirmed pCAP and vaccine-type (VT) CAP. VE in a subgroup of patients managed in the community was also estimated using a matched case-control design. VE was calculated as one minus the OR times 100%.

Results The overall VE of PCV13 was 33.2% (95% CI -106.6% to 82%) against pCAP irrespective of serotype and 38.1% (95% CI -131.9% to 89%) against VT-CAP in the cohort of adults ≥65 years. The VE was 42.3% (95% CI -244.1% to 94.7%) against VT-CAP in the age group at higher vaccine uptake. For the subgroup of cases managed in the community, the overall VE against disease due to any pneumococcal strain was 88.1% (95% CI 4.2% to 98.5%) and 91.7% (95% CI 13.1% to 99.2%) when we controlled for underlying conditions.

Conclusions Although our results are non-significant, PCV13 promises to be effective against all confirmed pCAP already with modest levels of uptake in the population of adults ≥65 years of age. Larger studies are needed to confirm the direct vaccine benefits.

Keywords PCV13, Pneumococcal conjugate vaccine, Vaccine effectiveness, Adult, Italy, Community-acquired pneumonia

Strengths and limitation of this study

- The test-negative method used in this study has reduced the risk for selection bias since both cases and controls were recruited in one process and arose from the whole population when the same enrolment criteria were met.
- The study was designed to capture CAP cases managed in the community, reducing the underestimate of the true impact of pneumococcal disease.
- The active surveillance of CAP was performed in a single regional setting leading to a small study size reducing the power to detect statistically significant effects.
- The test-negative method may have overestimated PCV13 VE if, by reducing the risk of acquiring vaccine-type serotypes, vaccination increases the risk of acquiring non vaccine-type serotypes as is likely to be the case if there is serotype replacement.

INTRODUCTION

Routine administration of the 7-valent conjugate vaccine (PCV7) since 2000 and of the second-generation conjugate vaccines (PCV10 and PCV13) since 2010 has resulted in an overall reduction in the rates of pneumococcal disease in both vaccinated and unvaccinated children, and indirectly among adults in several countries, owing to herd immunity.[1-2] However, the most recent available data suggest that significant burden still results from pneumococcal infection in older adults.

In the United States, the annual incidence of community-acquired pneumonia (CAP) requiring hospitalization in 2010-2012 was 24.8 cases (95% CI 23.5 to 26.1) per 10,000 adults 18 years of age or older, with a prevalence of pneumococcal disease of 5% and an incidence that was almost 5 times as high among adults 65 years of age or older as among younger adults.[3] In 2013, an estimated 10% of CAP cases in adults aged ≥65 years were caused by *S. pneumoniae* serotypes potentially preventable with the use of PCV13 in this population.[4]

In the UK, incidence of adult pneumococcal pneumonia declined over the 2008-2013 period, with serotypes included in PCV13 declining post-PCV13 introduction, suggesting an early herd protection effect from infant PCV13 on adult bacteraemic and non-bacteraemic disease. However, the most recent available data from 2012-2013 showed an incidence of 20.6 per 100,000 population for hospitalized adult pneumococcal CAP and 8.6 per 100,000 population for PCV13 serotype CAP.[5]

In Italy, high infant PCV13 coverage has been achieved since 2011 (vaccine uptake rate 90-95%).[6] For adults, only PPSV23 was recommended for routine immunization of those aged ≥65 years and at-risk individuals, but the vaccine uptake rates have been low to date. In recent years, some Italian regions have recommended PCV13 to adults with underlying diseases and to the elderly.[7]

Impact of PCV infant vaccination on adult pneumococcal pneumonia has not been well established in Italy. The hospitalization rates for pneumococcal pneumonia in the elderly population have remained relatively stable over the past decade, indicating a lack of herd protection amongst older age groups.[8]

In 2014, the CAPITA trial conducted in the Netherlands demonstrated the efficacy of PCV13 for the prevention, in those aged ≥65, of vaccine-type pneumococcal CAP.[9] Evidence from the CAPITA trial led to new ACIP PCV13 recommendations,[4, 10-11] of which a review is planned for 2018 owing to potential

changes in the epidemiological situation. In particular, studies evaluating the post-licensure effectiveness of PCV13 for prevention of invasive and non-bacteremic pneumococcal pneumonia among adults ≥65 years old using a case control design are needed.[11] This study attempts to address this unmet need.

We report findings of the direct impact of PCV13 from a two-year prospective study of a cohort of pneumococcal CAP adults.

Methods

From January 2013 until January 2015, a prospective, multicenter, population-based, active surveillance study of adults with CAP was conducted over two years in Apulia, a large Italian region of approximately 4,000,000 inhabitants. PPSV23 was introduced in Apulia in 2000 for use in adults aged ≥65 years and was replaced by PCV13 in November 2011 for adults aged 65, 70, and ≥75 years.[12] In 2015, the average vaccine uptake of PCV13 was 32% amongst adults aged 65-75 years (11 cohorts) and 10% in the overall population >75 years.[13]

According to 2013 census figures, the designated surveillance area included about 788,000 adults 65 years of age or older.[14] Patients were enrolled in two different study settings from a network of 31 sentinel physicians. Surveillance for suspected CAP was conducted by 16 treating physicians among patients presenting at 13 hospitals located in the region (a total of 13,841 patients aged ≥65 years admitted to Departments of Respiratory Medicine in 2013-2014) and by 15 general practitioners (GPs) providing primary care for a total of 5,010 persons aged ≥65 years throughout the region.

Adults ≥65 years with symptoms suggestive of lower respiratory tract infection were eligible for enrolment if they presented to a study hospital or to their GP for a clinical assessment; resided in the study region; had at least two of the eleven clinical criteria listed in Box 1; and had evidence of new infiltrates on chest radiography consistent with pneumonia.[15] Patients were excluded if they had been hospitalized recently (<10 days) or were functionally dependent nursing home, long-term care facility, or other institution residents (healthcare-associated pneumonia cases).

Box 1. Clinical criteria for definition of CAP

- New cough or sputum production
- Fever >38.0°C or hypothermia <36.1°C
- Chest pain
- Dyspnea
- Tachypnea
- New altered mental status
- Abnormal lung examination
- Respiratory failure
- Leukocytosis (>10 x109 white blood cells/liter or >15% bands) or leukopenia (<4.5 x109 white blood cells/liter)
- C-reactive protein value >3 times the upper limit of normal
- Hypoxemia with a partial oxygen pressure <60 mm Hg while the patient was breathing room air

Written informed consent was obtained from all the patients or their caregivers before enrolment. Study sentinel physicians used a standardised electronic Case Report Form to collect information regarding patient demographics, clinical information, microbiological investigations and status regarding receipt of pneumococcal vaccination; pneumonia severity was assessed using the CURB-65 score (Confusion, Urea >7 mmol/L, Respiratory rate ≥30 breaths/min, low systolic <90 mm Hg or diastolic ≤60 mm Hg Blood pressure, age ≥65 years). Patients were contacted 30 days after enrolment for outcome measures collection (30-day mortality, recovery with *sequelae*).

The study protocol was approved by the Institutional Review Board at the Apulian Regional Observatory for Epidemiology (PROT:18/OER/2012 February 20, 2012). The study was conducted according to the principles expressed in the Declaration of Helsinki.

Blood samples and nasopharyngeal swabs were obtained from the patients who presented to sentinel centers/GPs with symptoms of lower respiratory tract infection within 24 hours after presentation. In the case of patients with a productive cough, sputum was obtained. Bronchoalveolar-lavage (BAL) samples, blood-culture and sputum specimens that had been obtained for clinical care were sent to the Regional Reference Laboratory for Invasive Bacterial Diseases and analysed for the study.

S. pneumoniae was isolated by PCR and multiplex sequential PCR. Bacterial genomic DNA was extracted from 200 µl of biological samples using the QIAamp Dneasy Blood and Tissue kit (Qiagen), according to the manufacturer's instructions. Detection of *S. pneumoniae* was performed using a commercial multiplex assay (Pneumobacter ACE Detection for blood and Meningitis ACE Detection for CSF, Seegene; Sensitivity: detection limit of the Seeplex Pneumobacter Ace Detection = 10 copy/reaction − 10 copy/3 µl DNA). *S.*

pneumoniae serotyping was performed on PCR positive samples through a sequential multiplex PCR.[16] Twenty-nine primer pairs were designed to target serotypes 1, 3, 4, 5, 6 A/B, 7F, 7C, 8, 9V, 10A, 11A, 12F, 14, 15A, 15 B/C, 16F, 17F, 18, 19A, 19F, 20, 22F, 23F, 31, 33F, 34, 35B, 35F, and 38. A primer pair (primers cpsA-f and cpsA-r) was also included as an internal control targeting the cpsA (pneumococcal capsular polysaccharide synthesis gene) locus found in all pneumococci.[17] The amplified products, ranging from 250 bp to 988 bp, were analyzed by means of electrophoresis on a 2% agarose gel (Life Technologies) and visualization under UV light.

Patients with a positive PCR result for *S. pneumoniae* on blood/sputum/BAL were deemed to have pneumococcal CAP. Nasopharyngeal swabs samples were not used for the diagnosis of pCAP, due to the poor sensitivity and specificity previously reported.[3]

Vaccine Effectiveness analysis

To estimate the vaccine effectiveness (VE) of PCV13 in the prevention of pneumococcal CAP, a test-negative design was performed on cases enrolled during the study surveillance period. The analysis included two primary end points:

I. **VE in preventing confirmed pneumococcal CAP irrespective of serotype**, where cases were patients who had an episode of invasive or non-invasive pCAP due to any pneumococcal strain and controls were participants with an episode of non pneumococcal pneumonia;

II. **VE in preventing confirmed vaccine-type (VT) CAP**, where cases were patients with an episode of invasive or non-invasive pCAP due to vaccine-type strains and controls were patients with non-vaccine-type (NVT) pneumococcal CAP, non-typable isolates or non pneumococcal pneumonia.

These two end points were further assessed among patients who had underlying conditions.

The exposure of interest was vaccination with PCV13. The exposure to PPSV23 given <5 years prior to study enrolment was also assessed. Data were based on verified vaccine (both PCV13 and PPSV23) information and not self-report.

To further study the effectiveness of PCV13 in the prevention of episodes of confirmed pCAP managed in the community, post hoc analysis of a subgroup of cases reported by GPs network was performed. This

analysis was performed according to a 1:3 matched case-control design. For every enrolled patient, a list of potential asymptomatic controls was generated from GPs subjects' medical records. Three controls, matched by GP, age, and gender, were selected at random for each case. Controls were enrolled if they provided written informed consent to their GP. Study personnel contacted these GPs to obtain a medical and vaccination history for every control. Immunization information system was also used to verify vaccination histories.

Statistical Analysis

Statistical analyses were performed in STATA (version 14; StataCorp, College Station, TX, USA).

Chi-square analysis or Fisher's exact test, 2-sided, were used to calculate the p-value for the difference between study groups in percentages of subjects reporting a pCAP or non pneumococcal pneumonia.

Exact logistic regression was used to calculate the unadjusted odds ratios (ORs) of vaccination together with 95% confidence intervals (95% CI). In the post hoc subgroup analysis, the matched ORs for vaccination in cases and controls were calculated using conditional logistic regression, controlling for the presence of underlying conditions. Vaccine effectiveness was calculated as one minus the OR times 100%.

RESULTS

From the 1,867 eligible adults identified over the two-year period, 226 consented to the study. Main reasons why patients (or a relative) declined to participate were old age, difficulty in reading and/or understanding the invite letter, acute confusion or cognitive impairment, or a desire not to have medication altered. Of 226 patients recruited, 176 (77.9%) were admitted to Departments of Respiratory Medicine and 50 (22.1%) were registered with a GP. Pneumonia severity was low, moderate and high in 47 (20.8%), 167 (73.9%) and 12 (5.3%) adults, respectively. Forty patients were excluded as they were unable to provide a blood or a sputum/BAL sample, leaving 186 in the cohort for analyses. The median age of the cohort was 79 years (interquartile range, 73 to 85) and 65 (34.9%) were female. Twenty (10.8%) had received PCV13 and 60 (32.3%) had received PPSV23 <5 years prior to enrolment (Table 1). The seasonal distribution of CAP cases

followed a pattern similar to that of many other respiratory diseases, with similar peaks during the winter months of the two-year period (Figure 1).

Table 1. Characteristics of adults with community-acquired pneumonia requiring hospitalization or managed in the community

	Pneumococcal group (N = 59)	Non-pneumococcal group (N = 127)	CAP cohort (N = 186)
Demographics			
Age years	79 (71 to 83)	79 (73 to 85)	79 (73 to 85)
Male	42 (71.2)	79 (62.2)	121 (65.1)
Reporting			
Hospital physicians	38 (64.4)	105 (82.7)	143 (76.9)
GPs	21 (35.6)	22 (17.3)	43 (23.1)
Any underlying comorbidity*			
Chronic heart disease	28 (47.5)	70 (55.1)	98 (52.7)
Chronic respiratory disease	29 (49.2)	52 (40.9)	81 (43.6)
Diabetes	14 (23.7)	32 (25.2)	46 (24.7)
Chronic kidney disease	2 (3.4)	9 (7.1)	11 (5.9)
Chronic liver disease	2 (3.4)	3 (2.4)	5 (2.6)
Malignancy	0	4 (3.1)	4 (2.1)
Asplenia	1 (1.7)	1 (0.8)	2 (1.1)
Status regarding receipt of pneumococcal vaccination†			
PCV13	5 (8.5)	15 (11.8)	20 (10.8)
PPSV23 given <5 years prior to study enrolment	20 (33.9)	40 (31.5)	60 (32.3)
Outcomes§			
30-day mortality	2 (3.4)	2 (1.6)	4 (2.2)
Recovery with *sequelae*	5 (8.5)	20 (15.7)	25 (13.4)

Data are number, median (interquartile range) or number (%). *The groups were not mutually exclusive and therefore do not sum to 100%. †For both vaccines, patients were considered to be vaccinated if they had received the vaccine at least 2 weeks before enrolment. Data were missing for four patients in the non-pneumococcal group. One patient had received a dose of PCV13 ≥1 year after receipt of a PPSV23 dose given <5 years prior to study enrolment. §Data were missing for 20 patients in the pneumococcal group and 40 patients in the non-pneumococcal group.

A nasopharyngeal swab was obtained from 171 of the 186 (91.9%) participants, a blood sample from 152 (81.7%), a sputum specimen from 139 (74.7%), and a BAL specimen from 3 (1.6%). *S. pneumoniae* was detected in 71 (41.5%) nasopharyngeal swab, 2 (1.3%) blood, 55 (39.6%) sputum, and 2 (66.7%) BAL.

Of 186 in the CAP cohort, 59 (31.7%, 95% CI 25.7 to 38.9%) adults were identified as pneumococcal CAP. More than half (31, 52.5%) had disease caused by one of the PCV7 serotypes, of which 23F, 9V, 14, 4 and 19F were the most common; 8 (13.6%) had CAP due to additional PCV13 serotypes, of which 19A and 3 were the most common; 9 (15.2%) had CAP due to serotypes only contained in PPSV23; 4 (6.8%) had non-vaccine-type disease; 7 (11.9%) had nontypeable pneumococcal CAP (Figure 1). Five had received one dose

of PCV13 and 20 one dose of PPSV23 <5 years prior to enrolment. Of 39 patients infected with serotypes contained in PCV13, three had received this vaccine (disease caused by 9V in two cases and 23F in one) (Figure 2).

Baseline characteristics and outcomes were balanced between pneumococcal and non-pneumococcal groups (Table 1).

Vaccines Effectiveness

PCV13 VE estimate was 33.2% (95% CI -106.6% to 82%) against pneumococcal CAP irrespective of serotype and 38.1% (95% CI -131.9% to 89%) against vaccine-type CAP in the cohort of adults ≥65 years. The VE was 42.3% (95% CI -244.1% to 94.7%) with respect to VT-CAP in the age group at higher vaccine uptake (65-75 years).

The VE was 34.6% (95% CI -104.6% to 82.5%) against CAP due to any pneumococcal strain and 40.1% (95% CI -127.5% to 89.4%) against CAP due to vaccine-type strains for adults with underlying conditions.

PCV13 VE against the two primary end points in patients naïve to PPSV23 or vaccinated with PPSV23 ≥5 years prior to enrolment was 27.35% (95% CI -136.5% to 81.5%) and 17% (95% CI -234.7% to 85.9%) respectively, lower than VE estimates in subgroups defined irrespective of PPSV23 immune status (Table 2).

Table 2. PCV13 effectiveness estimates against all episodes of confirmed pneumococcal CAP and CAP due to vaccine serotypes in adults by vaccination status and the presence of underlying conditions

	Cases vaccinated/ unvaccinated	Controls vaccinated/ unvaccinated§	Vaccine effectiveness	95% CI
Pneumococcal CAP (any strain)	5/54	15/108*	33.2%	-106.6% to 82%
Vaccine-type CAP	3/36	17/126†	38.1%	-131.9% to 89%
Vaccine-type CAP in the age group at higher vaccine uptake (65-75 years)	2/14	8/32†	42.3%	-244.1% to 94.7%
Pneumococcal CAP in patients with ≥1 comorbid disorder	5/46	15/90*	34.6%	-104.6% to 82.5%
Vaccine-type CAP in patients with ≥1 comorbid disorder	3/31	17/105†	40.1%	-127.5% to 89.4%
Pneumococcal CAP in patients naïve to PPSV23 or vaccinated with PPSV23 ≥5 years prior to enrolment	5/34	14/69*	27.3%	-136.5% to 81.5%
Vaccine-type CAP in patients naïve to PPSV23 or vaccinated with PPSV23 ≥5 years prior to enrolment	3/19	16/84†	17%	-234.7% to 85.9%

*Controls were patients with an episode of non pneumococcal pneumonia. †Controls were patients with NVT pneumococcal CAP, non-typable isolates or non pneumococcal pneumonia. §Vaccine data were missing for four controls.

PPSV23 was not shown to have effectiveness against pneumococcal CAP in either all adults (VE -4%, 95% CI -115.4% to 50.4%) or those with comorbidities (VE -5.5%, 95 %CI: -130.5% to 52.2%) naïve to PCV13.

Post hoc subgroup analysis of 21 confirmed cases reported by GPs network (Table 1) provided estimates of PCV13 effectiveness in preventing pneumococcal CAP managed in the community.

We identified 4,965 asymptomatic adults as potential controls, of whom 129 (2.6%) died and 95 (1,9%) were excluded because they left the GP's practice during the study period. Among the remaining 4,741 controls, 63 (three per case) were selected for the analysis. Nine (14,2%) controls were replaced for difficulty in obtaining consent.

Review of GP records showed that the controls were of similar age and gender to cases, but differed in vaccination and clinical history: one case (4.8%) and one control (1.6%) had received PCV13 at least 2 weeks before enrolment, whereas 18 controls (28.6%) were vaccinated during the study period; 16 cases (76.2%) and 36 controls (57.1%) had at least one comorbid disorder.

The overall effectiveness of PCV13 against disease due to any pneumococcal strain was 88.1% (95% CI 4.2% to 98.5%) and 91.7% (95% CI 13.1% to 99.2%) when we controlled for underlying conditions (Figure 3).

DISCUSSION

To our knowledge, this is the first study to investigate the effectiveness of PCV13 for prevention of invasive and non-invasive pneumococcal pneumonia among adults ≥65 years. The overall VE was 33.2% against pCAP irrespective of serotype and 38.1% against VT-CAP. The VE was 42.3% against VT-CAP in the age group at higher vaccine uptake. Moreover, we estimated a vaccine effectiveness of 88.1% against confirmed pneumococcal CAP managed in the community, where most patients are treated as outpatients. Given that a substantial proportion of studies are based on hospitalised patients, the true burden of disease is not known in Europe, where only Finland, Spain and the UK have precise epidemiological data on CAP.[18-19]

In this study, PCV13 serotypes accounted for 66% of all confirmed pneumococcal CAP. National Invasive Bacterial Diseases surveillance data from Italy showed that, despite an uncertain reduction in the proportion of PCV13 serotypes in the period 2010–2012, these were still responsible for about 56% of cases among over-65s.[20] These data suggest that PCV13 vaccine-type pneumococcal disease continues to have a high burden in adults in Italy despite childhood PCV13 vaccination and would indicate a lack of herd protection effects in older age groups, in comparison to the vaccinated paediatric population.[8, 20-21] The most recent data in the UK suggest that, despite an ongoing trend of reduced incidence of PCV13 serotype CAP from paediatric conjugate vaccines,[5, 22] PCV13 serotypes currently account for 12.6% of all cases of CAP and 41% of pneumococcal CAP in adults.[18] In Ireland, in over 5 years following PCV13 introduction to routine childhood vaccination, the number of IPD associated with additional PCV13 serotypes in adults ≥65 years of age has remained relatively unchanged due to the persistence in serotypes 3 and 19A in this age-group.[23] In Spain, 13 years after introduction of PCV7/PCV13 for children, a significant proportion of adults continue to develop vaccine serotype CAP, suggesting an insufficient indirect protection. [24] Because it cannot be assumed that a decline in pneumococcal disease incidence observed in some countries will always be mirrored elsewhere in the same time, adults aged ≥65 years may have a great potential for disease reduction from PCV13 and may be a primary target of vaccination programmes.[9] This is particularly noteworthy for Italian population because the burden of CAP and pneumococcal disease in general is expected to increase with the aging society, even with the impact of childhood and adult vaccine programmes.[18, 25]

In our study, most of CAP was caused by PCV13 serotypes 23F, 9V, 14, 19A, 4, 19F, and 3 (Figure 2) that are among the less susceptible to antibiotics.[26] Recent findings for Switzerland showed that, while non-susceptible serotypes 19A, 9V, 6B, 23F and 14 among invasive and non-invasive *S. pneumoniae* decreased over time in patients up to age 64 years vaccination due to PCVs infant vaccination,[27-29] in patients older than 64 years with invasive *S. pneumoniae* resistance rates remained unchanged.[30] By preventing disease caused by resistant strains, adult PCV13 vaccination provides a robust strategy for combating antimicrobial resistance that is a growing problem in Europe.[31]

On January 19, 2017, PCV13 has been introduced into the routine vaccination schedule in Italy for all adults 65 years of age followed by a dose of PPV23.[32] The decision-making regarding its introduction was based on the CAPITA trial results and the ACIP recommendations, but also on a long history of experience of adult pneumococcal conjugate vaccination in some Italian regions including Apulia.[7, 12]

In this prospective cohort study of adults with CAP we found that PCV13 promise to be protective against all episodes of confirmed pneumococcal CAP (VE 33.2%) and against disease caused by serotypes contained in the vaccine (VE 38.1%). Recently published findings of the exploratory efficacy endpoint analysis of the CAPITA trial showed VE of 29% for all episodes of confirmed pneumococcal CAP and 43% for all non-bacteremic and noninvasive episodes of VT pneumococcal CAP,[33] findings consistent with the primary efficacy analysis.[9] On an ecological level, a preliminary analysis of hospitalization rates for adult pneumococcal CAP in Apulia region showed early PCV13 impact after the implementation of an adult vaccine programme (from 180,5 per 100,000 during 2006-2011 to 162,4 per 100,000 during 2012-2016; hospitalization risk ratio: 0,9 95% CI 0.83 to 0.97). [unpublished observations]

Moreover, our results showed that PCV13 promise to be effective for prevention of vaccine-type CAP already with modest levels of uptake in the target population (VE 42.3%). These data would suggest that rapid uptake and improved coverage of PCV13 among adults in the short term could maximize its impact.[11, 34]

The incidence of pneumococcal CAP is greatly increased in many individual clinical risk groups.[35] Since when the ACIP recommended PCV13 for immunocompromised adults in 2012, there remains little evidence regarding the efficacy of the vaccine in at risk populations.[36, 9, 37] Our findings would suggest that vaccination with PCV13 may be effective in preventing pneumococcal disease in adults ≥65 years with comorbid disorders. This observation, taken together with no effectiveness showed by PPV23 in our cohort, will require further studies to verify how adults with chronic diseases may fully benefit of the ACIP and the new Italian recommendations for the use of both PCV13 and PPSV23 in series. A recent systematic review and meta-analysis designed to estimate the efficacy of PPV23 in the prevention of pCAP, particularly in patients above 60 years of age and adults with underlying diseases, showed that PPV23 vaccination “alone”

does not demonstrate clear efficacy, supporting the administration of a dose of PCV13 first followed by a dose of PPV23 at least 8 weeks later.[38]

Another recent systematic review of the burden of vaccine preventable pneumococcal disease in UK adults did not identify studies that were conducted in the community, where the majority of pCAP is managed.[18] In our study, as it was designed to capture both invasive and non-invasive pneumococcal CAP, approximately 36% of cases had been reported by general practitioners, suggesting that hospital based studies may underestimate the true impact of pneumococcal disease. Post hoc subgroup analysis of cases managed in the community provided estimates of PCV13 effectiveness with respect to CAP from any pneumococcal serotype and this value did not change when we controlled for the presence of underlying disorders.

This study has several limitations. First, it was performed in a single region with a long-lasting history of experience of adult pneumococcal conjugate vaccination. Therefore, data from our setting may not be representative of the entire Italian adult population or generalizable to other settings. Moreover, data regarding the epidemiology of pCAP in adults in Italy are very limited and a large variability among published studies exists.[20]

Second, the recruitment rate was very low affecting the representativeness of the sample. The pre-study sample size calculation was 750 CAP cases aged over 64 years in the selected study area over a three years period of observation foreseen. We had estimated this sample size in the absence of a VE estimate as that provided by the CAPITA trial in 2014. As a reflection of the impact of stopping the study early (for administrative reasons), we had a much smaller recruitment than originally planned. However, there was not a risk for selection bias since both cases and controls were recruited in one process and arose from the whole population when the same enrolment criteria were met.

Third, 40 out of 226 enrolled patients were unable to provide a blood or a sputum/BAL sample, which could have led to underestimation or overestimation of pneumococcal aetiology rates. Owing to ethical and feasibility considerations, specimens were obtained only for clinical care and no invasive procedures were performed for this study, which may have reduced the microbiologic yield. However, 82% of the adults had at least one specimen type available for *S. pneumoniae* detection.

The study size was small reducing the power to detect statistically significant effects, although pneumococcal aetiology was identified in 31.7% CAP adults. Recent corresponding figure from Rodrigo et al. for UK was 29.3%.[5] The main limitation, however, pertains to the small numbers of PCV13 vaccinated cases and controls underlying the estimation of the vaccine effectiveness accounting for wide 95% CIs including zero. Although VE estimates should be interpreted with caution, our calculation reflected the still low PCV13 coverage achieved in the vaccinated cohorts. It was, therefore, too early to narrow the confidence limits around the point-estimate of effectiveness.

Fourth, the test-negative method may overestimate VE if, by reducing the risk of acquiring VT serotypes, vaccination increases the risk of acquiring NVT as is likely to be the case if there is serotype replacement.

Fifth, we were not able to assess the effectiveness of individual vaccine serotypes, as there were too few cases to allow statistical comparison between study groups.

Nonetheless, our study pointed out important gaps regarding the burden of pneumococcal CAP in Italy where there are limited data outside of national surveillance of IPD and the only available data for non-invasive disease are limited to hospitalization for pneumococcal pneumonia that, however, lack of serotyping information.[20] The active surveillance of adult confirmed CAP, drawn from a relative stable population over a two-year period, was a strength of our study and allowed us to estimate the effectiveness of the 13-valent pneumococcal conjugate vaccine against all confirmed CAP, without regard to serotype, the presence of underlying conditions, and the site of patient management (hospital/community).

This study has clinical practice implications for pneumococcal vaccination policies in adults in countries where PCV13 is becoming part of routine immunization of the elderly. Although our results are non-significant, they can stimulate to perform larger studies that would probably confirm the vaccine effectiveness but probably with narrower confidence intervals than those presented here.

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COMPETING INTERESTS

We have read and understood BMJ policy on declaration of interests and declare the following interests: RP reports grants from Pfizer, during the conduct of the study; grants, personal fees and non-financial support from Pfizer, personal fees and non-financial support from SanofiPasteurMSD, personal fees and non-financial support from GSK, outside the submitted work. DM reports grants and non-financial support from GSK, non-financial support from SanofiPasteurMSD, non-financial support from Pfizer, outside the submitted work. FF, MGC and MC declare that they have no competing interests.

SUPPORT STATEMENT

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CONTRIBUTORS

RP and DM conceptualised and designed the work, analysed and interpreted data, and writing the manuscript. FF and MGC contributed to the data collection, managed the database and provided statistical support. MC performed the laboratory work. All authors have read and approved the final manuscript.

DATA SHARING STATEMENT

There are no unpublished data available.

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Figure 1. Seasonal distribution of cases in the CAP cohort (N=186)

Figure 2. Number of cases of pneumococcal CAP by serotype and vaccination status (N=59)

Figure 3. PCV13 effectiveness (%) estimates against CAP due to any pneumococcal strain managed in the community*

* Fourteen cases (66.7%) had CAP caused by one of the PCV7 serotypes, of which 14 and 9V were the most common; three cases (14.3%) were due to additional PCV13 serotype 19A; three cases (14.3%) had CAP due to other serotypes; one (4.7%) had nontypeable pneumococcal CAP. One case vaccinated with PCV13 was caused by serotype 12F.

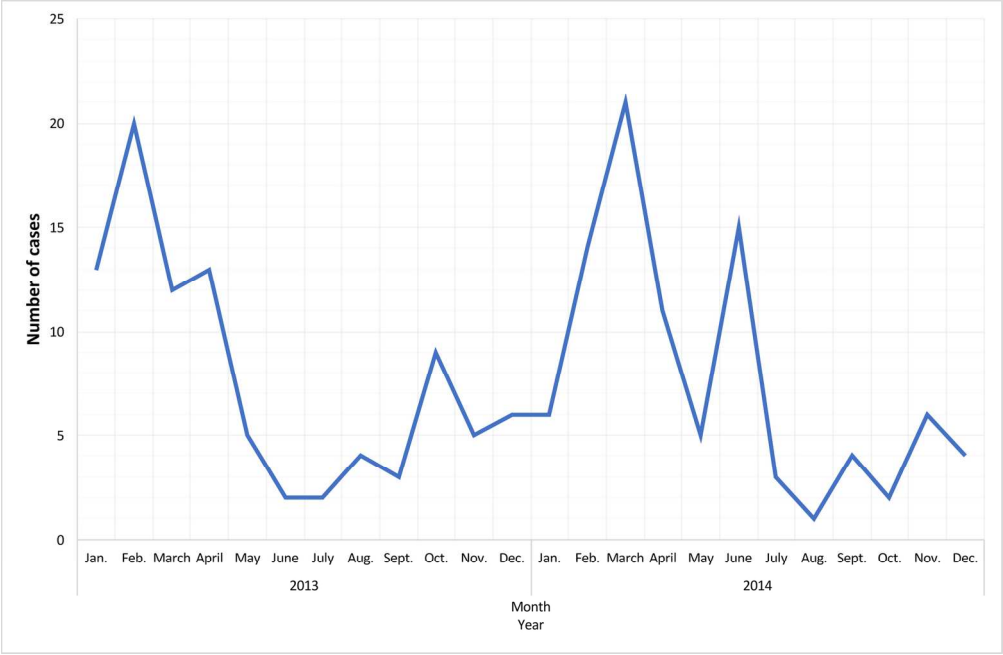

Figure 1. Seasonal distribution of cases in the CAP cohort (N=186)

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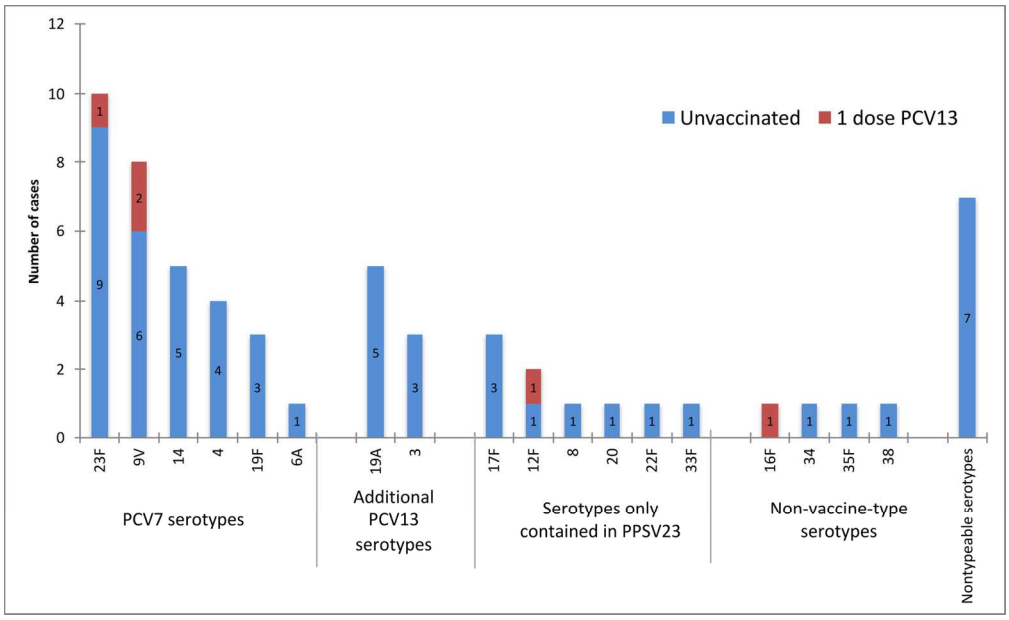

Figure 2. Number of cases of pneumococcal CAP by serotype and vaccination status (N=59)

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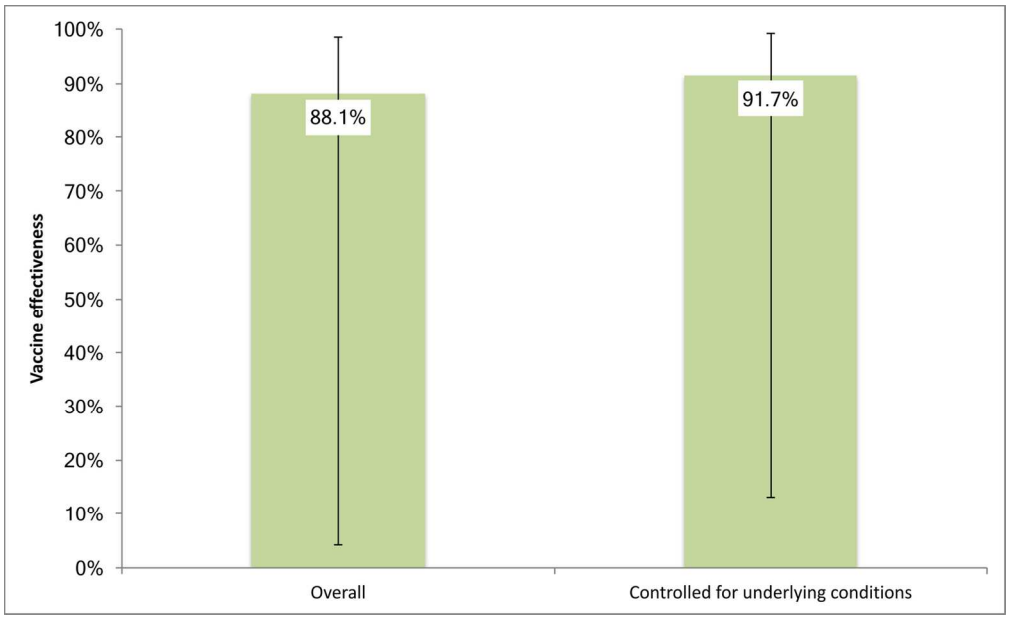

Figure 3. PCV13 effectiveness (%) estimates against CAP due to any pneumococcal strain managed in the community*

* Fourteen cases (66.7%) had CAP caused by one of the PCV7 serotypes, of which 14 and 9V were the most common; three cases (14.3%) were due to additional PCV13 serotype 19A; three cases (14.3%) had CAP due to other serotypes; one (4.7%) had nontypeable pneumococcal CAP. One case vaccinated with PCV13 was caused by serotype 12F.

156x95mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) If applicable, explain how loss to follow-up was addressed	8-9
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.