Evaluating Clinical Effectiveness of 13-Valent and 23-Valent Pneumococcal Vaccination among People Over 50 Years in Catalonia: The EPIVAC Cohort Study

Angel Vila-Corcoles* and Olga Ochoa-Gondar
Department of Primary Care, Institute of Catala de la Salut, Spain

Abstract
Pneumococcal disease is a major cause of morbidity and mortality worldwide. At present, two anti-pneumococcal vaccines are available for use in adults: the “classical” 23-valent Pneumococcal Polysaccharide Vaccine (PPSV23) and the “new” 13-valent Protein-Polysaccharide Conjugate Vaccine (PCV13). This paper describes rationale and design of the EPIVAC (Effectiveness of Pneumococcal and Influenza Vaccinations among Adults in Catalonia) Study, a population-based prospective cohort study with the major aim of evaluating possible clinical benefits from PPSV23 and PCV13 vaccinations in the general adult population over 50 years.

Introduction
Streptococcus pneumonia is a major cause of serious infectious illness among adults around the world. At present, a part of the classical 23-valent pneumococcal polysaccharide vaccine (PPSV23) that was marketed in 1983, a 13-valent pneumococcal conjugate vaccine (PCV13) is also available for using in adults since 2012 [1].

To date, the Advisory Committee on Immunization Practices (ACIP) of the Centres for Diseases Control and Prevention (CDC, Atlanta, Ga, USA) recommends PCV13 vaccination (sequentially with the PPSV23) for high-risk adults (basically anatomical or functional asplenia and immunocompromising conditions) and all persons 65 years or older (with or without risk conditions) [2,3]. These recommendations were based on several immunogenicity studies (which showed a good immune response in adults after PCV13) [4,5] and the results of the CAPITA study (a randomised-controlled trial [RCT] comparing PCV13 vs placebo among elderly individuals in the Netherlands) [6]. However, according to some observers, the ACIP recommendations for widespread use of PCV 13 in immunocompromised adults and in adults >65 years of age are based on very few supporting data [7].

In Catalonia, a region in North eastern Spain with approximately seven million people, the classical PPSV23 is recommended and publicly funded for high-risk adults and all elderly people since the 2000s, reaching a PPSV23 uptake of approximately 60% [8]. The PCV13 is recommended and publicly funded for some high-risk individuals (basically immunocompromised patients), being also prescribed by some clinicians for adults with other risk conditions (mainly chronic pulmonary or cardiac diseases) although it is not publicly funded in these patients [8].

Considering this, we designed a population-based cohort study, known as EPIVAC (Effectiveness of Pneumococcal and Influenza Vaccinations among Adults in Catalonia), with the major aim of evaluating possible clinical benefits of antipneumococcal and influenza vaccinations in the general adult population over 50 years in Catalonia. In addition, considering the debate about current vaccine’s recommendations, the study will also assess vaccination effectiveness in stratified analyses according to age subgroups (middle-aged and older adults) and immunological situation (immunocompetent and immunocompromised individuals).

Methodology
This is a population-based prospective cohort study involving all individuals ≥50 years-old registered in the 274 Primary Care Centres of the Catalanian Health Institute (2,025,000 individuals aged 50 years or older at 01/01/2015).

Cohort members will be followed since the beginning of the study (01/01/2015) until the
occurrence of any event, disenrollment from the PCC, death, or until the end of three-year follow-up). The study was approved by the ethical committee of the Institution (ethic committee IDIAP Jordi Gol, file P14/134) and will be conducted in accordance with the general principles for observational studies.

The Information system for the development of research in primary care of Catalonia (SIDIAP) [9] which compiles administrative data and clinical information contained in the Electronic PCC’s medical records will be used to identify vaccinations, comorbidities and underlying risk conditions among study subjects and to establish baseline characteristics of cohort members at study start (Table 1).

To identify study events (hospitalisations from invasive pneumococcal disease, pneumococcal pneumonia and/or all-cause pneumonia) occurred among cohort members across study period, we will use the national surveillance system for hospital discharge data (“Conjunto Minimo Basico de Datos”, CMBD) reported across study period from the 68 Catalonian hospitals.

Pneumococcal vaccination status (PPsV23 and PCV13) will be determined by reviewing PCC’s electronic clinical records, which contain specially designated fields for pneumococcal and influenza vaccinations (virtually all of them are administered at the PCCs in the Spanish Health System). Across the study period, pneumococcal vaccination status will be as a time-varying condition given some individuals can receive the vaccine after the study start.

Cox regression models for time-varying covariables will be used to evaluate the association between having received the PPVsV23/PCV13 and the time of the first outcome during the study period. Multivariable hazard ratios (HRs) adjusted for age, sex and comorbidities/underlying conditions will be calculated for each outcome measure. Vaccine effectiveness (VE) for both PCV13 and PPVsV23 will be estimated as VE=1-(1-HR)x100.

**Discussion**

Several years after its introduction in clinical practice, the effectiveness of anti-pneumococcal vaccination in adults remains controversial. Indeed, recommendations for pneumococcal vaccination in adults are not homogeneous according to distinct immunisation committees and or clinical guidelines [2,3,10-12]. If we consider classical PPVsV23, some countries recommend vaccination for all individuals aged 65 years or older (with or without risk conditions), whereas others recommend PPVsV23 vaccination starting at a younger or older age, and others recommend PPVsV23 only for high-risk individuals [10]. There is also heterogeneity for PCV13 recommendations and funding for adults in distinct settings [2,3,8,11,12].

Theoretically, the main advantage for the PCV13 is the fact that it may have better immunogenicity than PPVsV23, but a major shortcoming is the fact that it is directed against strains that are likely to be greatly reduced in the population since its introduction in childhood immunization. The PPVsV23 may provide poor immune response than PCV13 for common serotypes but, as major advantage, it may provide protection against ten additional serotypes [13].

If we consider the “classical” PPVsV23, several studies have reported a vaccine efficacy of approximately 40-60% against invasive pneumococcal disease among immunocompetent adults, but its efficacy/effectiveness against pneumonia remains uncertain (especially in at-risk population subgroups) [14,15]. If we consider the PCV13, apart from several immunogenicity studies [4,5] only a RCT (the CAPITA trial) has evaluated the clinical efficacy of this vaccine in adults to date [6]. This RCT investigated the clinical efficacy of PCV13 vs placebo among 85,000 adults aged 65 years or older in the Netherlands. It provided important data on PCV13 efficacy against vaccine-type pneumococcal pneumonia in elderly people, but some issues remain unanswered because PPVsV23 was not compared. Importantly, the CAPITA study was begun at a time that PCV was not recommended in children and, therefore, no suppression of PCV13 serotypes by the herd effect occurs; so, it cannot answer the question of whether PCV13 should be used routinely for adults in a country where PCV13 is widely used in children.

In the study setting (Catalonia, where PCV13 is routinely used in children since 2011) efforts were made to identify and establish a suitable and representative large cohort of middle-aged and older adults in whom PCV13/PPVsV23 could be evaluated and, as a result, the EPIVAC cohort study was planned. It should provide new evidence evaluating clinical effectiveness of PCV13 and PPVsV23, which may be helpful for future decisions about anti-pneumococcal vaccination strategies (changing or maintaining current PPVsV23 and/or PCV13 recommendations for adults). The EPIVAC study may also provide

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**Table 1: Criteria for identifying comorbidities and underlying risk conditions in the EPIVAC study cohort (on the basis on ICD-10 codes [International Classification of Diseases, 10th Revision] registered in primary care clinical records).**

<table>
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<tr>
<th>Comorbidity/Cause</th>
<th>ICD-10 Codes</th>
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<tr>
<td>Chronic pulmonary/respiratory disease: included chronic bronchitis/emphysema</td>
<td>J41-J44</td>
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<tr>
<td>Chronic heart disease: included congestive heart failure (I50), coronary artery</td>
<td>I20-I22, I25</td>
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<tr>
<td>Asthma (J45-J46) and/or other chronic pulmonary diseases (P27, E84, J47)</td>
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<td>Diabetes mellitus (E10-E14)</td>
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<td>Chronic liver disease: included chronic viral hepatitis (B18), cirrhosis (K74)</td>
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<td>and/or alcoholic hepatitis (K70)</td>
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<tr>
<td>Alcoholism (F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70)</td>
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<td>Smoking (F17)</td>
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<td>Anatomic or functional asplenia (D57,D73, Q89)</td>
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<td>Primary immunodeficiency (D80-D84)</td>
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<td>HIV infection (B20-B24)</td>
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<tr>
<td>Chronic renal disease: included nephrotic syndrome (N04, N39.1) and severe</td>
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<tr>
<td>chronic renal failure (N18-N19 with glomerular filtration rate ≤30 ml/min)</td>
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<td>Bone marrow transplantation (Z94)</td>
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<td>Cancer: included solid organ or haematological neoplasia (C00 to C97) diagnosed</td>
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<td>within previous 5 years.</td>
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<td>Immunosuppressive therapy: included long-term immunosuppressive medication and/</td>
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<td>radiotherapy in the previous 12 months (coded according to specific SIDIAP codes)</td>
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important considerations from the cost effectiveness analysis for immunisation programmes in the general practice.

We emphasize the importance of “vaccination effectiveness” data, and note the limited amount of such data regarding clinical efficacy/effectiveness of PCV13 in adults. Clinical outcomes of patients are affected by many factors, being antibody production and associated phagocyte stimulation only one aspect, which incompletely represent the immune response overall (especially aging immune response); so, RCT exclusively focused on immunogenicity/efficacy data may not adequately reflect the potential impact of vaccination on clinical outcomes [13].

After the introduction of routine PCV13 childhood immunisation in many countries, the potential value for both conjugate and polysaccharide vaccines for adults and elderly people could have decreased because of indirect effects from children vaccination. Thus, effectiveness and cost-effectiveness for both PPsV23 and PCV13 vaccination in adults should be updated and re-evaluated. In this way, considering the current debate about pneumococcal vaccine’s recommendations in adults, the EPIVAC cohort study will provide valuable population-based data evaluating PCV13 and PPsV23 effectiveness in a same population. Therefore, it would permit a better comparison of vaccination effectiveness and possible clinical benefits of vaccination from a public health point of view.

The EPIVAC study has been conceived and designed to investigate clinical effectiveness of anti-pneumococcal vaccination. Nevertheless, in addition to the primary objectives of the study, several sub study objectives are currently under development to maximise opportunities to learn about the health conditions in this population-based cohort.

Acknowledgments

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