

# A comparative public health and budget impact analysis of pneumococcal vaccines: The French case

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**Keywords:** budget impact analysis, epidemiological change, invasive pneumococcal diseases, pneumococcal polysaccharide vaccine, pneumococcal conjugate vaccine, public health

**Abbreviations:** ATIH, Agence Technique de l'Information sur l'Hospitalisation; BdM IT, Base des Médicaments et Informations Tarifaires; CNRP, Center National de Référence des Pneumocoques; COPD, chronic obstructive pulmonary disease; GHM, groupes homogènes de malades; GP, general practitioner; HCSP, Haut Conseil de la Santé Publique; HIV, human immunodeficiency virus; ICD, International Classification of Diseases; INED, Institut National d'Etudes Démographiques; INSEE, Institut National de la Statistique et des Etudes Economiques; IPD, invasive pneumococcal pneumonia; NBPP, non-bacteremic pneumococcal pneumonia; PCV7/13, 7-/13-valent pneumococcal conjugate vaccine; PMS, post-meningitis sequelae; PMSI, Program de médicalisation des systèmes d'information; PPV23, 23-valent pneumococcal polysaccharide vaccine; WHO, World Health Organization

In 2002, a pneumococcal conjugate vaccine (PCV) was introduced to French infants and toddlers. A change has been witnessed in the incidence of pneumococcal diseases in adults: the incidence of invasive pneumococcal disease (IPD) of serotypes covered by PCV decreased, and serotypes not covered by PCV increased. This study aimed to quantify the public health and budget impact of pneumococcal vaccination strategies in at-risk adults in France over 5 years. A previously published population-based Markov model was adapted to the French situation. At-risk adults received either PPV23 (pneumococcal polysaccharide vaccine; for the immunocompetent) or PCV13 (for the immunosuppressed). The strategy was compared to PCV13 alone. Uncertainty was addressed using extreme scenario analyses. Between 2014 and 2018, vaccination with PPV23/PCV13 led to a higher reduction in terms of IPD and non-bacteremic pneumococcal pneumonia cases avoided in most scenarios analyzed when compared to PCV13 alone. For budget impact, none of the scenarios was in favor of PCV13. Under conservative coverage assumptions, the total incremental budget impact ranged from € 39.8 million to € 69.3 million if PCV13 were to replace PPV23 in the immunocompetent. With the epidemiological changes of pneumococcal diseases and the broader serotype coverage of PPV23, the current program remains an optimal strategy from public health perspective. Given the additional budget required for the use of PCV13 alone and its uncertain public health benefits, vaccination with PPV23 remains the preferred strategy.

## Introduction

### *Streptococcus pneumoniae*

*Streptococcus pneumoniae* is a gram-positive bacterium, of which more than 90 distinct serotypes have been identified.<sup>1</sup> Infection with the bacterium can lead to life-threatening diseases, such as pneumonia, meningitis and bacteremia. *S. pneumoniae* is also associated with non-invasive form of diseases, including non-bacteremic pneumococcal pneumonia (NBPP), which accounted for approximately 80% of the burden of pneumococcal pneumonia.<sup>2–5</sup>

Pneumococcal diseases lead to approximately 1.6 million deaths annually in the world, most in infants, children and the elderly.<sup>6</sup> In France, the annual number of pneumococcal infection cases was estimated at 455,000, and deaths from these diseases were between 3,500 and 11,000. In terms of invasive pneumococcal diseases (IPD), the number of cases was reported to range between 6,000 and 7,000.<sup>7</sup>

Individuals with predisposing factors are more likely to contracting pneumococcal infection. Chronic pulmonary, cardiac, renal and hepatic diseases and immunosuppression are considered as risk factors.<sup>2–4,6,8</sup>

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### Vaccination against pneumococcal diseases

Vaccination is the only public health measure that is likely to reduce the burden of pneumococcal diseases.<sup>4</sup> Currently, 2 types of vaccines are licensed, pneumococcal polysaccharide vaccines (PPV) and pneumococcal conjugate vaccines (PCV).

In France, the 23-valent PPV (PPV23; Pneumo 23<sup>®</sup>, Sanofi Pasteur MSD) is indicated in the prevention of pneumococcal infections caused by serotypes included in the vaccines in individuals aged 2 years and older who are at risk.<sup>9</sup> The 13-valent PCV (PCV13; Prevenar 13<sup>®</sup>, Pfizer), which replaced the 7-valent vaccine (PCV7; Prevenar<sup>®</sup>, Pfizer) in 2010, is indicated in the prevention of IPD, pneumonia and acute otitis media in those aged between 6 weeks and 17 years (in those between 6 weeks and 5 years from 2010 and expanded to between 6 weeks and 17 years from 2013), as well as in the prevention of IPD in those aged 18 years old or older (in those aged 50 years and above from 2011 and expanded to 18 years and above from 2013).<sup>10-12</sup>

In Europe, recommendation on the use of PPV in at-risk adults and/or the elderly dates back to the 1980s.<sup>13</sup> For infants and toddlers, many European countries introduced routine childhood vaccination programs using PCVs.<sup>13</sup> In 2013, HCSP (*Haut Conseil de la Santé Publique*; High Council of Public Health) updated its recommendation to introduce the sequential use of PCV and PPV in certain at-risk populations aged 5 years and older: the immunosuppressed, those with nephrotic syndrome, those with a cerebrospinal fluid leak, those with a cochlear implant and those who are candidates for such implant. The recommendation for the immunosuppressed and the asplenic was made based on immunogenicity data of PCVs and hyporesponsiveness risk assumed for PPV23.<sup>14</sup> Nevertheless, the recommendation has not considered the epidemiological change induced by childhood vaccination with PCVs (see the following section). PPV23 is

recommended in other high-risk populations, including those with heart, pulmonary and renal failure, those with chronic hepatic diseases, those with severe asthma under continuous treatment, and those with diabetes not sufficiently by diet.<sup>15</sup> Revaccination with the same vaccine is not recommended, regardless of risk group.

### The impact of vaccinating infants and toddlers on the epidemiology in adults

In France, infants and toddlers are vaccinated with 3 or 4 doses of PCV13. It is estimated that, in those born in 2011, 96.1% received the first vaccine dose at 6 months of age and 88.8% received at least 3 doses at 2 years of age (end of 2013 data).<sup>16</sup>

The routine vaccination of infants and toddlers with PCV not only affects the epidemiology in children, changes have also been observed in adults in the UK,<sup>17</sup> the US,<sup>18</sup> Germany<sup>19</sup> and Spain.<sup>20</sup>

As a herd immunity effect, the incidence of IPD associated with the serotypes covered in PCV decreased in adults. However such reduction has been offset by serotype replacement: an increase in the incidence of IPD associated with the serotypes not covered in PCV.<sup>17-20</sup> In France, the data from CNRP (*Center National de Référence des Pneumocoques*; National Reference Center for Pneumococcus) showed a marked increase in the proportion of IPD associated with non-PCV serotypes overtime (Emmanuelle Varon, personal communication; the data have been reported graphically in the CNRP Report 2011<sup>21</sup>).

### Objectives

With the move from PCV7 to PCV13 in France in 2010, it is expected that the epidemiology of pneumococcal diseases may be further affected. In light of the expansion of the indication of PCV13, the current study aimed to assess the comparative public health and budget impact of vaccinating at-risk adults in France with different strategies (i.e. PPV23 for the immunocompetent, PCV13 for the immunosuppressed; PCV13 alone), in the context of epidemiological changes. Several scenario analyses were carried out in order to address the uncertainties around vaccine effectiveness, costs and epidemiology.

## Results

### At-risk population and vaccination coverage

French at-risk population eligible for vaccination against pneumococcal diseases (9.5 million) was tracked over time. Approximately 80% of these individuals were aged 50 years and older. Between 2014 and 2018, a total of 1.95 million people received the vaccination.

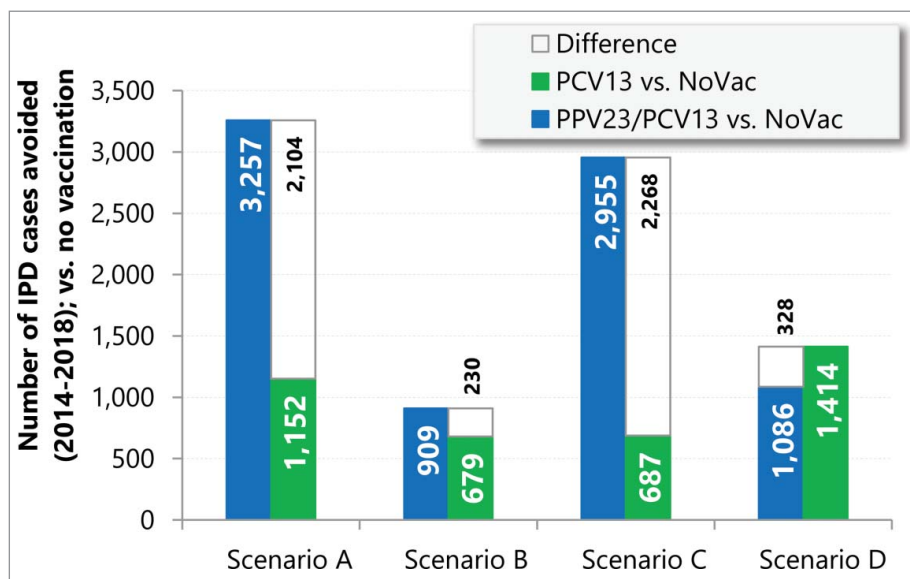


Figure 1. Number of IPD cases avoided over 2014-2018 period.

**Table 1.** Definition of at-risk adults.<sup>15</sup>

The immunosuppressed	The Immunocompetent
<ul style="list-style-type: none"> <li>◆ Patients with asplenia or hyposplenia (including sickle cell disease)</li> <li>◆ Patients with hereditary immunodeficiency</li> <li>◆ Patients with HIV infection, regardless of the immune status</li> <li>◆ Patients receiving chemotherapy for solid tumors or hematologic malignancies</li> <li>◆ Patients with a solid organ transplant or on the waiting list of solid organ transplantation</li> <li>◆ Patients with hematopoietic stem cell transplantation</li> <li>◆ Patients receiving immunosuppressive biotherapy and/or corticosteroids for chronic autoimmune or inflammatory disease</li> <li>◆ Patients with nephrotic syndrome</li> </ul>	<ul style="list-style-type: none"> <li>◆ Patients with cyanotic congenital heart disease or heart failure</li> <li>◆ Patients with chronic respiratory failure, chronic obstructive pulmonary disease (COPD) or emphysema</li> <li>◆ Patients with severe asthma, who receive continuous treatment</li> <li>◆ Patients with renal failure</li> <li>◆ Patients with chronic liver disease, of alcoholic origin or not</li> <li>◆ Patients with diabetes who are not controlled by simple regimen</li> <li>◆ Patients with cerebrospinal fluid leak or with cochlear implant</li> </ul>

**Public health impact**

Vaccinating the immunocompetent individuals with PPV23 and the immunosuppressed individuals with PCV13 (referred to as PPV23/PCV13 hereafter) was associated with the greatest decrease in the total number of IPD cases over the period between 2014 and 2018, in all 4 scenarios except scenario D (Fig. 1; also Table S6). When compared to vaccination with PCV13 alone, the strategy led to favorable outcomes in 3 of 4 scenarios, ranging from 230 (−1.1%; calculated as the difference divided by the total number of IPD cases under PCV13 only strategy, the same below) additional cases avoided in scenario B to 2,268 (−8.4%) additional IPD cases avoided in scenario C. In scenario D, where higher efficacy was assumed for PCV13, the additional IPD cases avoided was 328 (1.6%) under the PCV13 only strategy.

In terms of the total number of NBPP cases, PPV23/PCV13 led to a decreased or unchanged number when compared to PCV13 alone in scenarios A, B and C. In scenario D, where higher efficacy was assumed for PCV13, the number of cases avoided increased by 10,145 (+9.7%) when comparing PCV13 to PPV23/PCV13. The cumulative number of PMS (post-meningitis sequelae) cases followed the same pattern as that of IPD.

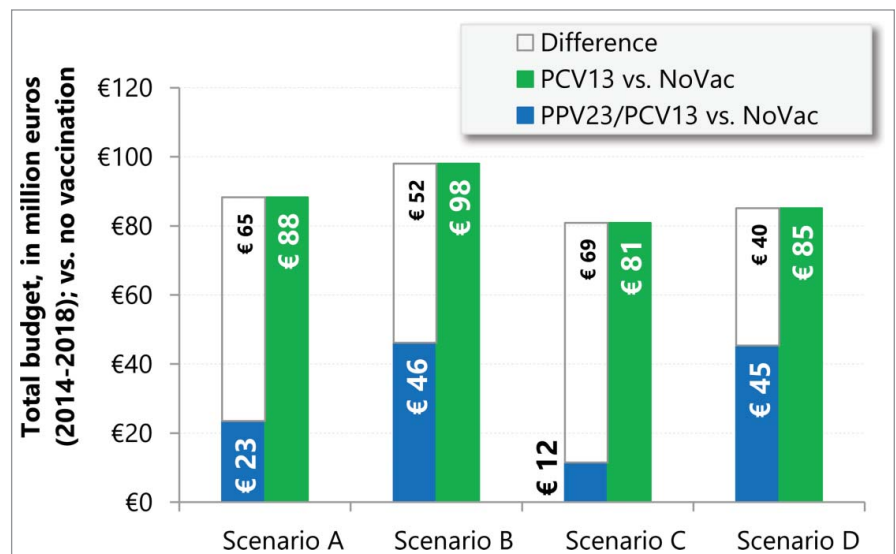
**Budget impact analysis**

From 2014 to 2018, vaccination with PCV13 alone was associated with the highest costs across 4 scenarios. Even in scenario D, the most favorable scenario for PCV13, the incremental cost was estimated at € 39.8 million (+15.2%; calculated as the

difference divided by the total budget under PPV23/PCV13 strategy). In other scenarios, such increment ranged between € 51.9 million (+19.7%; scenario B) and € 69.3 (+19.0%; scenario C), when compared to the use of PPV23/PCV13 (Fig. 2; Table S7).

**Sensitivity analyses**

Sensitivity analyses have been carried out for costs except for the price of vaccines (doubling or halved), vaccination coverage (1.25 times or halved) and the prevalence of risk factors (using the UK source<sup>22</sup>). The results did not change qualitatively but only quantitatively (Table S8).



**Figure 2.** Comparative budget impact analysis over the 2014-2018 period.

**Table 2.** Clinical and demographical parameters.

Parameter	Base case values
<b>Incidence of IPD</b> <sup>29,30^</sup>	See Figure 3
<b>Proportions of the target population in each risk group</b> <sup>22,33,39-52</sup>	See Figure 4
<b>Risk of developing IPD (compared with the adult population)</b> <sup>22,29,30^</sup>	<b>18-64 years</b> AR i.c.: 5.754 / AR i.s.: 1.437
	<b>≥65 years</b> AR i.c.: 10.864 / AR i.s.: 3.746
<b>Herd protection effect: decrease in incidence of IPD associated with PCV serotypes (cumulative gamma distribution)</b> <sup>16,29,30^*</sup>	<b>18-64 years</b> α: 0.9759; β: 2.7966
	<b>≥65 years</b> α: 0.7464; β: 4.7585
<b>Serotypes replacement effect: increase in incidence of IPD associated with non-PCV serotypes (cumulative gamma distribution)</b> <sup>16,29,30^*</sup>	<b>18-64 years</b> α: 3.1406; β: 0.5763
	<b>≥65 years</b> α: 0.5664; β: 14.0359
<b>Incidence of NBPP (per 100,000 person-years)</b> <sup>32-34</sup>	231.4
<b>Proportion of meningitis in IPD</b> <sup>^^</sup>	7.6%
<b>Proportion of meningitis patients with PMS</b> <sup>31</sup>	31.7%
<b>Case-fatality rate by age group: IPD</b> <sup>32</sup>	18-64: 10.2%
	≥65: 31.5%
<b>Case-fatality rate: NBPP</b> <sup>32</sup>	3.1%

\* The change in the incidence of IPD in adults is estimated as  $\frac{1}{\Gamma(\alpha)} \gamma\left(\alpha, \frac{x}{\beta}\right)$ , where x is gamma function, γ is the lower incomplete gamma function and x is the cumulative vaccination rate in infants and children. ^ Emmanuelle Varon, personal communication. ^^ Agnès Lepoutre, personal communication

AR: at-risk adults; i.c.: immunocompetent; i.s.: immunosuppressed; IPD: invasive pneumococcal disease; NBPP: non-bacteremic pneumococcal pneumonia.

**Table 3.** Scenario analysis.

		Scenario A		Scenario B		Scenario C		Scenario D	
		PPV23	PCV13	PPV23	PCV13	PPV23	PCV13	PPV23	PCV13
<b>Vaccine efficacy / effectiveness</b>	Against IPD (vaccinated serotypes), AR i.c.	82% 25,54	76% 25	32% 25,54	46% 25	90% *	90% 25	32% 25,54	90% 25
	Against IPD (vaccinated serotypes), AR i.s.	35% 55	35% **	1% 55	1% **	69% 55	69% **	1% 55***	69% 55***
	Against NBPP (all serotypes), AR i.c.	39% 56	24% 25	0% ****	0% 25	64% 65	46% 25	0% ****	46% 25
<b>Disease related costs</b>		-		-20%		+20%		-20%	
<b>Change in IPD incidence in adults over time</b>	PCV13 not PCV7	No change		No change		Decrease		No change	
	Not PCV13	Increase		No change		Increase		No change	

\* Assumed to be the same as PCV13. \*\* Assumed to be the same as PPV23. \*\*\* The upper and lower limits from the reference. \*\*\*\* Assumed to be 0.

AR: at-risk adults; i.c.: immunocompetent; i.s.: immunosuppressed; IPD: invasive pneumococcal disease; NBPP: non-bacteremic pneumococcal pneumonia.

## Discussion

### Summary of findings

In the current analysis, the public health and budget impact of using different vaccination strategies were assessed in the French context. Epidemiological changes of IPD induced by routine infant and toddler vaccination were taken into account in the analysis. Due to uncertainties around such changes, as well as around efficacy due to a lack of head-to-head studies, 4 scenario analyses were devised, with one extreme scenario (D) that favors PCV13.

The strategy with PCV13 alone was only found to render more public health benefits in scenario D, where higher efficacy was assumed. It was associated with the highest cost across scenarios. The additional cost (when compared to PPV23/PCV13) amounted to between € 39.8 million and € 69.3 million.

### Strengths

As our previous studies,<sup>23,24</sup> the current analysis considered the epidemiological changes of IPD stemmed from routine infant and toddler vaccination. Indeed, a clear trend has been witnessed across countries that the use of PCVs in infants and toddlers would provide an indirect herd effect on adults, leading to a reduced value of using such vaccines in the adult population.

Secondly, the study employed recently published data from CAPiTA study of PCV13,<sup>25</sup> which improved the scientific evidence. However, there is still a lack of head-to-head studies comparing the 2 vaccines. In order to address uncertainties, 4 scenarios were considered, with some of them favoring PCV13.

Lastly, French data were used whenever possible, especially the data on the prevalence of risk factors. Although English and Welsh national data<sup>22</sup> were also used to fill the data gaps, the comparable estimates from the 2 populations followed the same trend.

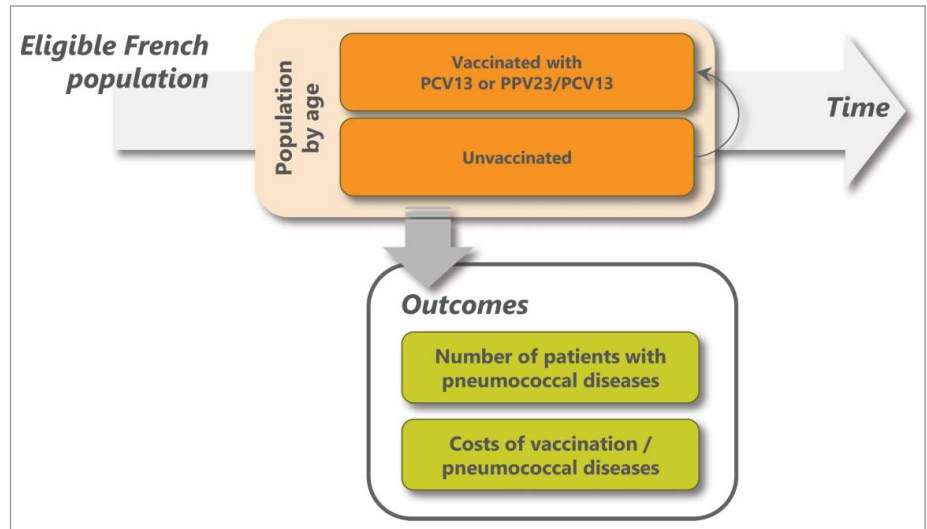


Figure 3. Model schematics.

### Limitations

Firstly, the current analysis did not fully reflect the French recommendation since it was not possible to model the sequential use of PPV and PCV in the immunosuppressed due to a lack of data and the limitation of the model structure. Nevertheless the size of the immunosuppressed population was small and the conclusion will not be changed qualitatively. Furthermore, the target population was included only adults (vs. those aged 5 years or older in the recommendation) and proxies were used to calculate the size of the target population.

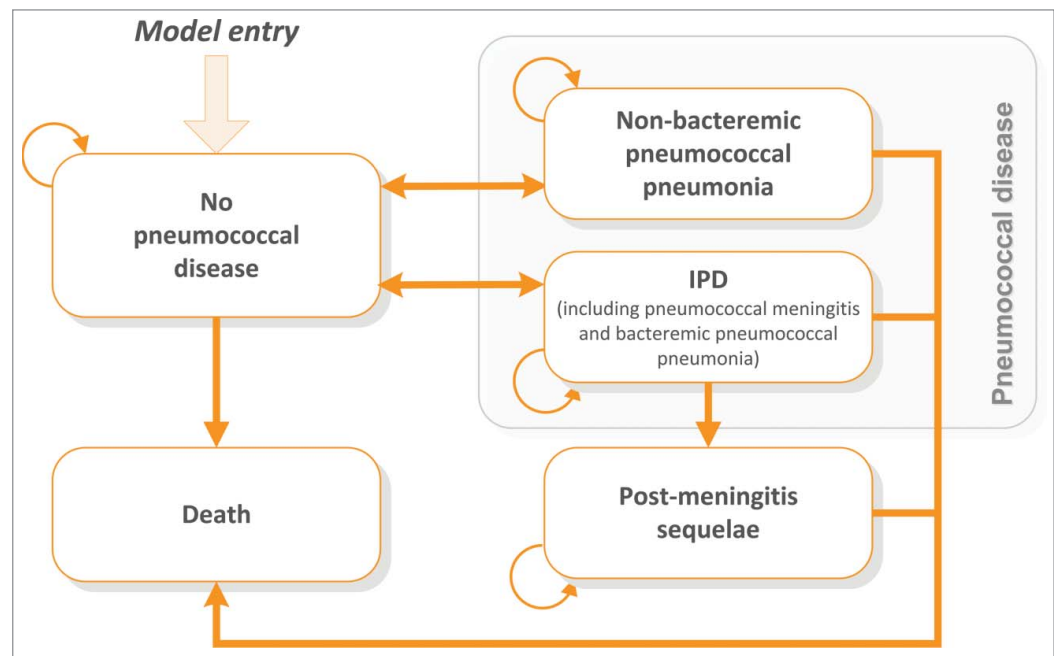


Figure 4. Model structure.

**Table 4.** Waning function.

Year since the initial vaccination	Value (of initial effectiveness) <sup>57,58</sup>
1	82%
2	78%
3	72%
4	64%
5	54%
6	43%
7	30%
8	15%
9 and more	0%

As an infectious disease, the current analysis only adopted a static approach and it did not capture the dynamics of transmission of pneumococcal infections therefore the benefits of vaccination may not be reflected wholly.

Thirdly, the model has not distinguished case-fatality rates across serotypes. A Danish study has reported that serotypes 10A, 11A, 15B and 17F are associated with an elevated case-fatality rate, to which PPV23 was shown to induce a robust immune response.<sup>26,27</sup>

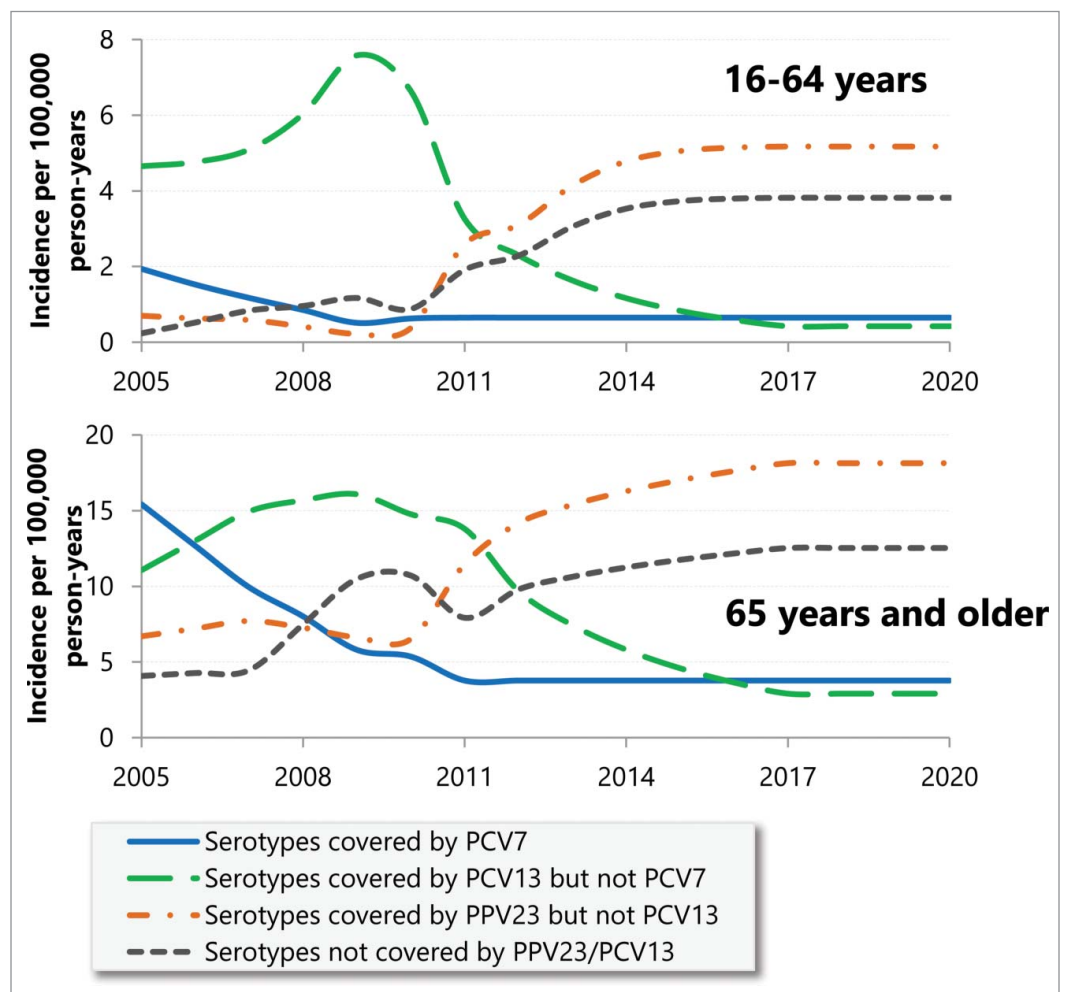
Fourthly, although best efforts were made to identify French data, there was still missing information that could not be found. This related to the incidence of NBPP, which contributes to a large proportion of the burden of pneumococcal diseases. Similarly, the prevalence of risk factors was retrieved from various sources, which might lack consistencies. More research is required to update current study.

Fifthly, the current analysis adopted a time horizon of 5 years, which is arguably not long enough to forecast the future public health benefits from vaccination. However the epidemiology will further change due to continued serotype replacement and herd effect, which may make the

**Table 5.** Costs.

Parameter	Base case values*
Cost of vaccine (1 dose) <sup>59**</sup>	PPV23: € 8.81; PCV13: € 36.87
Administration <sup>60,61</sup>	€ 15.10
Pneumococcal pneumonia and hospitalized NBPP, per episode <sup>62,63</sup>	€ 3,601
Meningitis, per episode <sup>62,63</sup>	€ 5,636
Non-hospitalized NBPP, per episode <sup>59,61,64</sup>	€ 33
PMS, per year <sup>60</sup>	€ 8,000

\* Values used in the model, from the perspective of the French health insurance. \*\* Accounted for co-payment (65%). NBPP: non-bacteremic pneumococcal pneumonia; PMS: post-meningitis sequelae.

**Figure 5.** Observed and projected epidemiological changes among adults and elderly in serotype-specific incidence of IPD induced by vaccination of infants and toddlers.

forecast inaccurate. Therefore it might be prudent to have a limited time horizon, and update the analysis when future information is made available.

Additionally, the estimation of the absolute number of IPD cases did not involve any back calculation, and the actual burden was -therefore conservatively underestimated.

### Concluding remarks

This study has demonstrated that a combination of PPV23 for the at-risk immunocompetent adults and PCV13 for the at-risk immunosuppressed adults is likely to afford better protection to these populations compared to the use of PCV13 alone. With the switch from PCV7 to PCV13 in the routine vaccination of infants and toddlers, further changes in the epidemiology of IPD are expected. The extended use of PCV13 in children has substantially restricted its public health impact in adults because of the change in the serotype distribution of pneumococcal diseases.<sup>28</sup> Therefore the value of broader serotype coverage by PPV23 is of the most importance. Considering the additional budget required for the use of PCV13 alone, vaccination of immunocompetent individuals with PPV23 remains the preferred strategy.

Close and continued monitoring of the disease is required to update the current analysis. Other epidemiological parameters are also needed to refine the results.

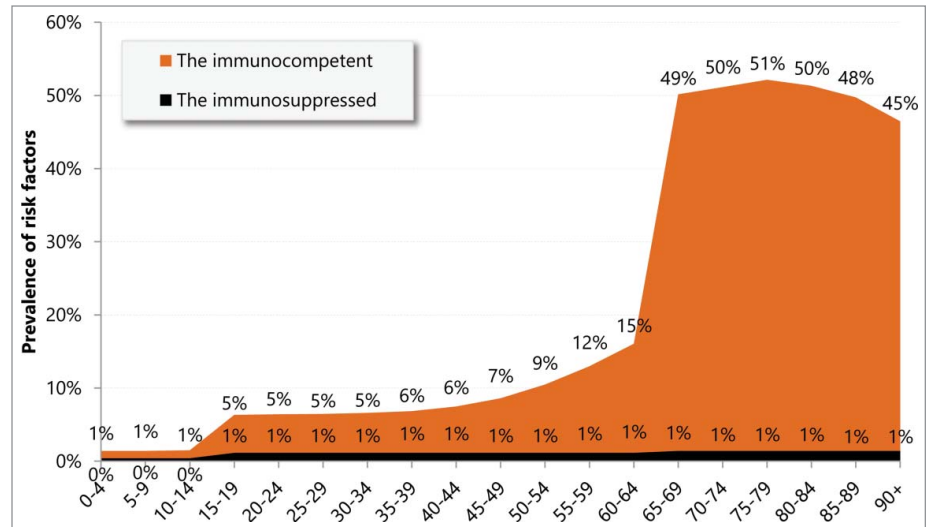
## Materials and Methods

### Model structure

The current model was adapted from the previous analysis developed for Germany.<sup>23</sup> It was a population-based, multiple cohort Markov model which tracked at-risk French adults. They could receive a vaccine or remain unvaccinated.

Incident cohorts of the adults who are at-risk in the first calendar year were tracked until they reached 100 years old, die, or until 2018. The model recorded the number of disease cases and costs. The model schematics are presented in **Figure 3**.

**Figure 4** describes the model structure. For all cohorts, with or without vaccination, adults with no pneumococcal disease could develop IPD (pneumonia or meningitis) or NBPP, or stay without pneumococcal disease. Those with meningitis might develop PMS if they survived meningitis. Those who recovered from IPD or NBPP may contract pneumococcal diseases for a second time. Due to the rarity, those with PMS were assumed not to develop another episode of IPD or NBPP. Excess mortality (expressed as case-fatality rate) associated with IPD and NBPP was considered in the model. The mortality rate was assumed to be the same for all other health states, as for the general population.



**Figure 6.** Prevalence of risk factors in the French population.

The model had a cycle length of one year and the results were presented for the period between 2014 and 2018. In order to account for those vaccinated before 2014, the model was initiated in 2005.

### Target population and assessed strategies

The analyses considered at-risk adults (immunocompetent or immunosuppressed) and did not take into account those aged below 18 years. The risk factors included followed the HCSP recommendation,<sup>15</sup> and are presented in **Table 1**.

Three strategies were considered in the analysis, vaccination with PPV23/PCV13, vaccination with PCV13 alone and no vaccination. Sequential vaccination (with 2 different vaccines over a short period of time) was not considered due to the lack of data on efficacy and the limitation of the model structure. Following the study question, the incremental results are presented for PPV23/PCV13 vs. PCV13 alone. The results of the no vaccination strategy are presented in the Online Appendix.

Revaccination (with the same vaccine over a long period of time) was not considered since not recommended by HCSP.<sup>15</sup>

### Invasive pneumococcal diseases

As noted earlier, the analysis considered changes in the epidemiology of IPD. Since the introduction of PCV vaccination in infants and toddlers, a herd immunity effect has been witnessed in adults, as well as a serotype replacement effect.<sup>21,29</sup>

To model such changes, the incidence of IPD between 2005 and 2011 was retrieved from the EPIBAC (Agnès Lepoutre, personal communication) and the serotype split in 2005, 2007, 2009, 2010 and 2011 from CNRP (Emmanuelle Varon, personal communication; the CNRP Report 2012<sup>29</sup>).

In France, PCV13 replaced PCV7 in 2010 in the French vaccination program of infants and toddlers.<sup>30</sup> Since the last dose of PCV was given at the 24 months old, the analysis assumed that the effect of PCV7 will last until 2011. Therefore the effect of

PCV7 on the epidemiology of IPD was assumed to be captured by the CNRP data. From 2012, it was assumed that the incidence of IPD associated with 6 serotypes covered by PCV13 but not PCV7 would decrease, of IPD associated with other serotypes would increase and of IPD associated with 7 serotypes covered by PCV7 would remain stable. Using the same approach as in previous studies,<sup>23,24</sup> it was assumed that the proportion change in the incidence of IPD was a function of the cumulative vaccination rate in children,<sup>16</sup> following the same pattern as observed for PCV7. A cumulative gamma distribution was selected because of the goodness of fit. The aforementioned changes were applied for a period of 6 years, as per the observed data of PCV7. The analysis applied constant incidence beyond this period. The incidence between 2005 and 2020 is presented in **Figure 5** and the parameters in **Table 2** (Emmanuelle Varon, personal communication; the CNRP Report 2012<sup>29</sup>).

It should be noted that no back calculation has been performed to account for existing PPV23 vaccination. Nevertheless the approach was conservative because there was an underestimation of the number of IPD cases in the no vaccination scenario, leading to a downwards bias in the effectiveness of vaccination.

The incidence of IPD was adjusted for the at-risk population, since the aforementioned incidence was for the overall population. Due to a lack of information, a national study conducted in England and Wales was utilized.<sup>22</sup> The case-fatality rate from IPD was also based on this study due to a lack of French data. In the model, 7.6% of IPD cases were meningitis, based on average incidence from the French EPI-BAC dataset (Agnès Lepoutre, personal communication). The rate of post-meningitis sequelae came from an international meta-analysis.<sup>31</sup>

#### Natural course of other pneumococcal diseases

No publication was found reporting the incidence of NBPP in France. The estimation was done based on the incidence of hospitalized pneumonia and the hospitalization rate (32%) from the UK.<sup>32</sup> The incidence of hospitalized pneumonia was calculated using the French hospital database ATIH (*Agence Technique de l'Information sur l'Hospitalisation*; Technical Information Agency on Hospitalization).<sup>33</sup> The data consisted of all pneumonia due to *S. pneumoniae* (ICD-10 J13) and pneumonia, organism unspecified (ICD-10 J18), of which 37.2% were attributable to *S. pneumoniae*.<sup>34</sup> The case-fatality rate was also based on the UK data, which reported that 9.6% for hospitalized cases and 0% for outpatient cases.<sup>32</sup>

#### Demography

Population size and life tables (by age and over time) were obtained from the INSEE (*Institut National de la Statistique et des Etudes Economiques*; National Institute for Statistics and Economic Studies) and INED (*Institut National d'Etudes Démographiques*; National Institute for Demographic Studies).<sup>35-38</sup>

The proportion of the at-risk population for vaccination by age group was estimated from French sources.<sup>33,39-52</sup> When

French data were not available, the data from England and Wales were used.<sup>22</sup> The prevalence of risk factors is presented in **Figure 6**.

Vaccine coverage was derived using the actual and projected sales data of PPV23,<sup>53</sup> and the size of the target population. Between 2014 and 2020, approximately 4.0% of the at-risk adults would receive the vaccination annually.

#### Vaccine efficacy and effectiveness

Four scenarios have been considered for vaccine efficacy and effectiveness due to a lack of head-to-head comparison between PPV23 and PCV13 (**Table 3**). In scenario A (point estimates derived from published literature), absolute vaccine efficacy of PCV13 against IPD vaccine type-related in the immunocompetent population was based on recently published results from the CAPiTA study.<sup>25</sup> For PPV23, its comparative efficacy versus PCV13 was derived using an indirect comparison (placebo as the common comparator), utilizing the data synthesized in a Cochrane review.<sup>54</sup> For efficacy against IPD in the immunosuppressed, the estimate came from a clinical trial of patients infected with HIV.<sup>55</sup> The effectiveness against NBPP in the immunocompetent was retrieved from the Spanish EVAN-65 study.<sup>56</sup> No effectiveness was assumed against NBPP in the immunosuppressed. In scenario B, favorable efficacy estimates were assumed for PCV13 while in scenario C, for PPV23 (assuming vaccination provides limited protection in both scenarios). In scenario D, the highest estimates from the previous 3 scenarios were used for PCV13 while lowest for PPV23.

The aforementioned vaccine efficacy waned over time for both vaccines since there is no long-term follow-up date for PCV13. It was assumed that there was no more protection 8 years after the initial vaccination (**Table 4**).<sup>57,58</sup>

#### Costs

Costs were estimated from the perspective of the French health insurance, *Assurance Maladie*. All costs were estimated in 2013/4 and expressed in euros (**Table 5**). The costs were not discounted due to the nature of the study.

The unit price of PPV23 and PCV13 were retrieved from BdM IT (*Base des Médicaments et Informations Tarifaires*; Basic Drugs and Tariff Information), € 13.56 per one dose of PPV23 and € 56.72 per one dose of PCV13 (retail price, VAT included).<sup>59</sup> Both vaccines were reimbursed at 65%. One visit to a general practitioner (GP) was assumed for the administration, based on a cost-effectiveness analysis of meningococcal B vaccine published by HCSP.<sup>60</sup> One GP visit cost € 23, of which 70% was reimbursed and the patients were required to pay € 1 flat fee (*participation forfaitaire*) in addition.<sup>61</sup>

All IPD cases were hospitalized and the cost was retrieved from the PMSI (*Program de médicalisation des systèmes d'information*; Program of Medicalization of Information Systems) database,<sup>62,63</sup> using the weight average cost of pneumonia and common pleuritis in adults (GHM 04M05) for pneumonia, € 3,600.85 per case, and central nervous system infection except



viral meningitis (GHM 01M05) for meningitis, € 5,636.37 per case.

For hospitalized NBPP, the above cost of invasive pneumonia was used. For outpatient cases, 2 GP visits and 10 day of co-amoxiclav (1g t.i.d.; € 7.28 for 8 sachets of 1g co-amoxiclav, reimbursement rate 65%) were assumed.<sup>64</sup> The cost was therefore calculated at €32.85 from the perspective of health insurance.<sup>59,61</sup>

Lastly, a case of PMS would incur an annual cost of € 8,000, based on the aforementioned HCSP study on the cost-effectiveness of a meningococcal vaccine.<sup>60</sup>

### Public health and budget impact

In the analysis, the number of IPD and NBPP cases over time, the cumulative number of PMS cases, total costs and costs by category over time were reported. The public health and budget impact were estimated as the difference between the assessed strategies, i.e., between PPV23/PCV13 and PCV13 only. The public health and budget impact was estimated for 4 scenarios with different assumptions on efficacy, costs and epidemiological changes (Table 3). Additional deterministic sensitivity analyses were also conducted for costs (doubling or halved; except for the price of vaccines), vaccination coverage (1.25 times or halved) and the prevalence of risk factors (UK source<sup>22</sup>).

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### Disclosure of Potential Conflicts of Interest

This study was conducted by Amaris and funded by Sanofi Pasteur MSD. Yiling Jiang, Frédéric Gervais and Aline Gauthier are employees of Amaris, which received consulting fees from Sanofi Pasteur MSD. Charles Baptiste, Prescilla Martinon and Xavier Bresse are employees of Sanofi Pasteur MSD. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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### Supplemental Material

Supplemental data for this article can be accessed on the publisher's website.

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