Public Health Impact of Implementing the 20-valent Pneumococcal Conjugate Vaccine for Routine Paediatric Vaccination in Belgium

Annick Mignon [a], An Ta [b], Evelien De Sutter [a], Aleksandar Ilic [c], Johnna Perdrizet [d], Sophie Warren [e]

[a] Pfizer Belux, Pleinlaan 17, 1050 Brussels, Belgium
[b] Cytel, London, United Kingdom
[c] Pfizer UK, Tadworth, United Kingdom
[d] Global Value and Evidence, Pfizer Canada, Kirkland, QC, Canada
[e] Pfizer, 1 Portland Street, Cambridge, MA 02139, USA

aleksandar.ilic@pfizer.com

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Abstract
Objective
In 2024, serotypes covered by 20-valent pneumococcal conjugate vaccine (PCV20) were among the most prevalent in invasive pneumococcal disease (IPD) in Belgium. This study assessed the public health impact of implementing PCV20 into Belgium's paediatric national immunization programme (NIP) over 10 years and foregone public health benefits of delayed PCV20 implementation versus the current standard of care – 13-valent PCV (PCV13).

Methods
A Markov structure comprising of active disease, non-disease, and death states estimated IPD, inpatient- and outpatient-pneumonia, and otitis media (OM) cases and deaths for each vaccine over 1, 2, and 10 years. This population-based study considered a vaccinated cohort (<2 years), and unvaccinated cohorts benefiting from indirect effects. The base-case included only individuals aged <18 years. Several scenarios were tested including indirect effect exclusion and exploring serotype replacement.

Results
Over 10 years, PCV20 was estimated to prevent 185,512 more disease cases and 30 more deaths versus PCV13. Delaying PCV20 implementation by one year resulted in 8,141 disease cases that could have been prevented, more than doubling in second year. PCV20 health gain was reduced in scenarios without indirect effects or with serotype replacement, though PCV20 remained favoured in all scenarios.

Conclusions
Paediatric PCV20 implementation could have greater public health benefit in Belgium compared to PCV13 and a 2-year delay in PCV20 implementation could result in substantial foregone public health gains. A limitation of this study is that the base case did not account for serotype replacement due to limited evidence, although scenario analyses suggest that the overall conclusions are robust.

Introduction

The history of pneumococcal conjugate vaccine (PCV) implementation in the paediatric national immunisation programme (NIP) of Belgium differs from that of most European countries, beginning with the successive implementation of 7-valent PCV (PCV7; covering serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) between 2007 and 2011 (1). After Belgium introduced PCV7 using a 2+1 dosing schedule (two primary doses and one booster), the incidence of invasive pneumococcal disease (IPD) decreased substantially among children <2 years old, particularly for infections caused by PCV7 serotypes (2). However, a surge in incidence of disease caused by non-PCV7 serotypes, especially serotype 19A, prompted a switch from PCV7 to the 13-valent PCV (PCV13; covering PCV7 serotypes plus 1, 5, 7F, 3, 6A and 19A) in 2011. PCV13 successfully reduced PCV13-type IPD cases, including >90% reduction in serotype-19A-related cases among children aged <2 years (2, 3).

The Belgian Superior Health Council (SHC) later recommended both PCV13 and the 10-valent PCV (PCV10; covering PCV7 serotypes plus 1, 5 and 7F) for inclusion in the Belgian paediatric NIP, with a full transition to PCV10 in 2015/2016 due to low circulating PCV13-type disease, reduced PCV13 serotype carriage, and lower vaccination costs (1, 3). This programmatic change caused IPD incidence and the proportion of disease caused by serotypes 3, 6A, and 19A in Belgian children to increase between 2016 and 2018 (1, 4). Consequently, PCV13 was reintroduced into the Belgian paediatric NIP in 2019, remaining the current standard of care (SoC) since (5).

Surveillance data from the 2024 Belgian National Reference Case Report revealed that serotypes 8, 22F, and 12F were among the most prevalent serotypes detected in IPD isolates among all age groups, being reported among 11.5%, 4.1%, and 14.6% of all isolates, respectively (6). These serotypes are covered exclusively by new higher-valent PCVs, including the 15-valent PCV (PCV15; covering PCV13 serotypes plus 22F and 33F) and the 20-valent

PCV (PCV20; covering PCV15 serotypes plus 8, 10A, 11A, 12F and 15B). In 2025, the advisory report of the Belgian Superior Health Council (SHC) on pneumococcal vaccination for children reported PCV20 serotypes caused 59% of all IPD cases, compared to only 14% and 19% caused by PCV13 serotypes in children aged <2 years and <16 years, respectively (5). The unique serotypes in PCV20 also contributed to an additional 37.9% (n = 7 cases) of meningitis cases in young children compared with PCV13. In March 2024, PCV20 received marketing authorization for paediatric use in a 3+1 schedule by the European Commission (EC) (7).

Considering Belgium's epidemiological data and the recent approval of paediatric PCV20, the SHC recently updated the paediatric pneumococcal vaccination advice (5). The SHC now recommends PCV20 for routine vaccination of healthy children in Belgium since it offers extended coverage against 20 pneumococcal serotypes and can potentially increase protection against serious infections such as meningitis, septicaemia, and pneumonia (5). Although PCV20 has been recommended by SHC, the vaccine has yet to be implemented in the NIP. Therefore, the aims of this analysis were twofold: [1] assess the public health impact of implementing PCV20 3+1 into Belgium's paediatric NIP versus PCV13 2+1 in children aged < 18 years and [2] assess the public health impact of delayed implementation of PCV20 versus continued PCV13 use over 1 and 2 years.

Methods

Modelling approach

This study applied a deterministic modelling approach using a previously-published Microsoft Excel® based Markov model to assess the impact of different PCVs on the public health burden of pneumococcal disease (8-15). The model comprised three mutually exclusive health states (an active pneumococcal disease state, a non-disease state, and a death state) and applied fixed probabilities and inputs to determine how individuals move through the model. In the active pneumococcal disease state, individuals could experience IPD, inpatient and outpatient pneumonia, and otitis media (OM) events. The model estimated disease cases and associated deaths over a 10-year period for each vaccination strategy: PCV20 under a 3+1 schedule and PCV13 under a 2+1 schedule (7).

This population-based study modelled a vaccinated cohort of children aged <2 years eligible for pneumococcal vaccination (benefiting from direct vaccine effects) and an unvaccinated cohort aged 2-17 years (benefiting from indirect vaccine effects) during the modelled time horizon. Populations were categorised into six age groups: <1 year, 1 year, 2 years, 3 years, 4 years, and 5–17 years.

To reflect real-world vaccination practice, the analysis adopted a multiple-cohort approach which allowed new birth cohorts to enter the model and become eligible for vaccination annually from Year 2 to Year 10 of the time horizon.

Model inputs

Population size and probability of death (i.e., general mortality) were obtained from official Belgian sources (Table 1) (16). Annual birth cohort sizes were calculated using crude birth rate data from the United Nations and projected population data from official Belgian sources (Table 2) (16-19).

Belgium-specific data were used to obtain epidemiological inputs, where such data was available (Table 3). IPD incidence for children (<18-year-olds) was based on the 2017-2018 (PCV10 period) data from Desmet et al., 2021, while IPD incidence for >18-year-olds (only used for a scenario analysis) was based on the 2023 data from Cuypers et al., 2024 (1, 20). Data for non-invasive inpatient pneumonia, outpatient pneumonia, and OM were sourced from Beutels et al., 2011 (21). IPD incidence data and the breakdown of IPD cases into meningitis and bacteraemia were sourced from Cuypers et al. 2024 and Desmet et al. 2021, respectively (1, 20). Non-invasive diseases were defined more broadly as all-cause disease (i.e. pneumonia or otitis media caused by any infectious agent, including bacteria, viruses, fungi, or parasites). Incidence rates of non-invasive disease stratified by age group were calculated based on data from Beutels et al. 2011 (21). Case fatality rates of IPD (meningitis and bacteraemia) and inpatient pneumonia were based on data from Beutels et al. 2011, whereas no increased risk of mortality was assumed to be associated with outpatient pneumonia and OM (21).

The 2024 IPD serotype coverage data stratified by age group were sourced from the National Reference Centre Report (Figure 1) (6). Vaccine uptake for all vaccines and schedules was assumed at 93.8% for the priming series and booster doses (22).

The model assumed that PCV20 would have comparable effectiveness to lower-valent PCVs, such as PCV7 and PCV13. Direct vaccine effects against IPD were based on a PCV13 real-world effectiveness study conducted in Europe, in which PCV13 effectiveness in a 2+1 vaccination schedule was estimated at 78.2% and effectiveness in a 3+1 schedule was estimated at 89.7%.

TABLE 1: Belgian population data (16).

POPULATION BY AGE GROUP	
Age group, years	**Population size**
<1	117,375
1	117,375
2	117,375
3	117,375
4	117,375
5–17	1,740,051
18–34*	2,465,420
35–49*	2,279,003
50–64*	2,335,638
≥65*	2,356,665

*Data for adults were used in scenario analyses.

TABLE 2: Belgian new birth cohort input data (16-19).

NEW BIRTH COHORT BY YEAR	
Year	**Number of infants aged <1 year**
Year 1	117,375
Year 2	117,071
Year 3	117,884
Year 4	118,131
Year 5	118,687
Year 6	119,137
Year 7	119,157
Year 8	119,271
Year 9	119,486
Year 10	119,805

TABLE 3: Epidemiology inputs.

Age group, years	Disease incidence per 100,000 individuals (1,20,21)				Breakdown of IPD cases, % (1)		Case fatality rate, %* (21)		
	IPD	Inpatient pneumonia	Outpatient pneumonia	OM	Meningitis	Bacteraemia	Meningitis	Bacteraemia	Inpatient pneumonia
<1	58.40	1,161.00	1,500.00	14,000.00	13.80	86.20	6.60	1.00	0.04
1	58.40	912.00	1,500.00	14,000.00	3.50	96.50	11.30	0.00	0.00
2	11.20	912.00	1,500.00	14,000.00	3.50	96.50	11.30	0.00	0.00
3	11.20	912.00	1,500.00	14,000.00	3.50	96.50	11.30	0.00	0.00
4	11.20	912.00	200.00	14,000.00	3.50	96.50	11.30	0.00	0.00
5–17	11.20	113.65	200.00	2,500.00	9.15	90.85	2.66	1.50	0.49
18–34§	15.67	58.13	247.28	-	6.29	93.71	8.68	9.69	0.25
35–49§	15.67	92.43	309.82	-	6.29	93.71	8.91	15.80	0.66
50–64§	15.67	145.00	390.90	-	6.29	93.71	7.73	13.43	1.04
65+§	35.22	869.15	940.62	-	4.65	95.35	23.22	23.19	2.43

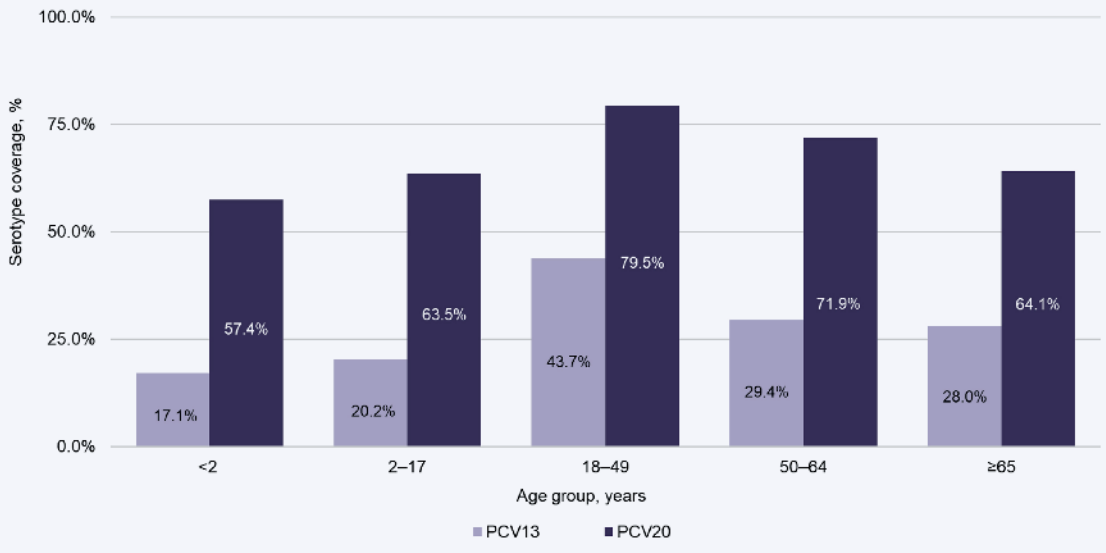
* No disease-related fatality was assumed for outpatient pneumonia and OM.
§ Data used in scenario analysis only. Abbreviations: IPD, invasive pneumococcal disease; OM, otitis media

Therefore, the model assumed PCV13 2+1 had 78.2% vaccine effectiveness against IPD and PCV20 3+1 had 89.7% effectiveness against IPD (Table 4) (23-25). The study applied an average vaccine effectiveness estimate across serotypes, consistent with similar studies in the literature, as serotype-specific estimates of effectiveness have inherent limitations due to small sample sizes and real-world data are not yet available for the 7 additional serotypes unique to PCV20 (26-30). To account for potentially lower effectiveness in the first year of life, prior to completion of the full schedule, vaccine effects for <12-month-olds were reduced by 67.0% (2+1 vaccine schedule) and 75.6% (3+1 vaccine schedule) of the full vaccine effects (31). Additionally, based on published evidence, the effectiveness of all vaccines waned 10% each year beginning in Year 6, with a maximum protection duration of 10 years (23, 32).

Due to lack of multi-site studies investigating PCV13 effectiveness against non-invasive diseases, this study opted for an "efficacy-based" approach using PCV7 efficacy data. The model assumed PCV13 and PCV20 had the same efficacy as reported in the PCV7 clinical trials, regardless of schedule. Therefore, effectiveness against all-cause inpatient pneumonia, outpatient pneumonia, and OM was assumed to be 25.5%, 6.0%, and 7.8%, respectively, then further adjusted to account for differences in serotype coverage in present-day Belgium to those of PCV7 serotypes during the time of the PCV7 trials (24, 25).

The model assumed that, after several years of inclusion in the paediatric NIP, the serotypes covered by PCV13 had reached a steady state. Therefore, the model only considered indirect (herd) vaccine effects in children 2-17 years for the newly

FIGURE 1: Serotype coverage by age group (6).



Percentage labels represent the serotype coverage by vaccine in 2024

Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine

TABLE 4: Vaccine effectiveness parameters.

Analysis	Direct effect, %				
	Vaccine schedule (23)	Vaccine effectiveness	All-cause inpatient pneumonia (24)	All-cause outpatient pneumonia (25)	All-cause OM (25)
Deterministic analyses	2+1 (PCV13)	78.2	25.5	6.0	7.8
	3+1 (PCV20)	89.7			
Scenario analyses	2+1 (all vaccines)	88.7			

Vaccine	Indirect effect accrual, %[a] (33,34)				
	Year 1	Year 2	Year 3	Year 4	Year 5+
PCV13[b]	100.0	100.0	100.0	100.0	100.0
PCV20	37.5	52.8	67.7	82.7	100.0

Age, years	Indirect effect, %				
	Maximum reduction				Vaccinated adult population excluded from indirect benefits, %
	IPD (33-34)	All-cause inpatient pneumonia[c] (34-37)	All-cause outpatient pneumonia[c] (35,36)	OM[d] (34,38)	
<17	83.0	30.5	22.5	20.0	-
18–64[e]	88.0	15.0	-	-	-
≥65[e]	73.0	15.0	-	-	45.6

a. Estimates were informed by Ladhani et al. 2018, comparing PCV13 minus PCV7 serotypes (excluding serotype 3) in PCV7 period (2010) to post PCV13 (2011–2017) (34). Year 6 of the PCV13 infant program was chosen as the steady-state year per Perdrizet et al. 2023 (33). **b.** 100% indicates that the maximum incidence reductions were achieved, and a steady state was established. **c.** For children, data from Levy et al. 2017 were adjusted for IPD serotype distribution as reported in Janoir et al. 2016 at the time of PCV13 introduction in 2009 (35,36). For adults, data from Rodrigo et al. 2015 were adjusted for IPD serotype distribution as reported in Ladhani et al. 2018 at the time of PCV13 introduction in 2009 (34,37). **d.** Data from Lau et al. 2015 were adjusted for IPD serotype distribution as reported in Ladhani et al. 2018 at the time of PCV13 introduction in 2009 (34,38).

Abbreviations: IPD, invasive pneumococcal disease; OM, otitis media; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine.

covered serotypes in PCV20 and no further benefits or additional protection against PCV13 serotypes would be observed. Indirect vaccine effect against IPD was sourced from Ladhani et al. 2018 and Perdrizet et al. 2023, and data for inpatient pneumonia, outpatient pneumonia, and OM were sourced from other European impact studies (Table 4) (33-38). Based on IPD data from the United Kingdom (UK), indirect effects were assumed to develop gradually over time with disease rates stabilizing by year 4 of implementation into the Belgian paediatric NIP (33, 34). Details regarding indirect vaccine effect estimations have been discussed in previous studies (8-10, 12).

Deterministic analyses

Two deterministic (fixed input) analyses were run, each designed to address one of the two main study goals. The main analysis considered the health impacts of all PCV strategies in Belgian children up to 18 years of age over the 10-year time horizon. Health outcomes included the number of cases and associated deaths, broken down by type of clinical event for each vaccine strategy. These outcomes were then used to calculate the difference in results between PCV20 and PCV13.

Additional analyses looked at how delaying PCV20 implementation over periods of 1 and 2 years would affect public health of Belgian children compared the continued use of PCV13. Number of disease cases and deaths were estimated to show the potential immediate consequences of postponing PCV20 adoption in the Belgium paediatric NIP.

Scenario analyses

Uncertainties from the model's assumptions and inputs were examined by testing the following scenarios, each looking at outcomes over 10 years:

– **Scenario 1**: German data were used to assess uncertainty in the estimates for non-invasive disease incidence (39-41). German data were used due to its geographical proximity to Belgium, comprehensiveness of data, and its use in recently published models (10).

– **Scenario 2**: Assumed a 0% vaccine effect for PCV20 in the first year of life against serotypes that did not meet non-inferiority criteria compared to PCV13 in the PCV20 3+1 clinical trial (3, 4, 9V, 23F, and 12F). Since real-world data show that vaccine effect does not perfectly correlate with immunogenicity data, we assumed lower vaccine effect for those serotypes (42-45).

– **Scenario 3**: Included indirect protection for the entire Belgian population ≥18 years, to capture potential underestimation of including only the paediatric population. In this scenario, 45.6% of the population aged ≥65 years were assumed to be vaccinated (46). These individuals did not benefit from indirect effects to avoid overestimation of impact.

– **Scenario 4**: A conservative approach assumed 0% indirect protection for all ages. Indirect effects were included in the base case as substantial evidence has demonstrated that childhood PCV programs have reduced vaccine-type carriage and disease in both vaccinated and unvaccinated populations (47-49).

– **Scenario 5 and 6**: Assumed an annual, linear reduction of 5% (moderate replacement) and 10% (high replacement) in incidence of PCV20-specific serotypes, and corresponding increases in non-vaccine serotypes, to model serotype replacement. While serotype replacement has been observed after the introduction of previous PCVs, historical evidence (e.g., PCV7 to PCV13) suggested diminished magnitude over time, possibly due to the lower invasiveness of residual serotypes (Løchen et al., 2020) (50). As such, the extent of serotype replacement following PCV20 remains uncertain, however these scenario were intended to model potential replacement.

– **Scenario 7**: Assumed the implementation of PCV20 under a 2+1 schedule, in which scenario the model used direct vaccine effect against IPD of 88.7% for all vaccines and a <12-month direct vaccine effect modifier of 67% (23).

Results

Deterministic results

The estimated public health impact of PCV20 versus PCV13 in the Belgian paediatric population over 1 year, 2 years, and 10 years of implementation is presented in Table 5 and Figure 2.

FIGURE 2: Impact of a 2-year delay in the introduction of PCV20 on disease burden in Belgian children.

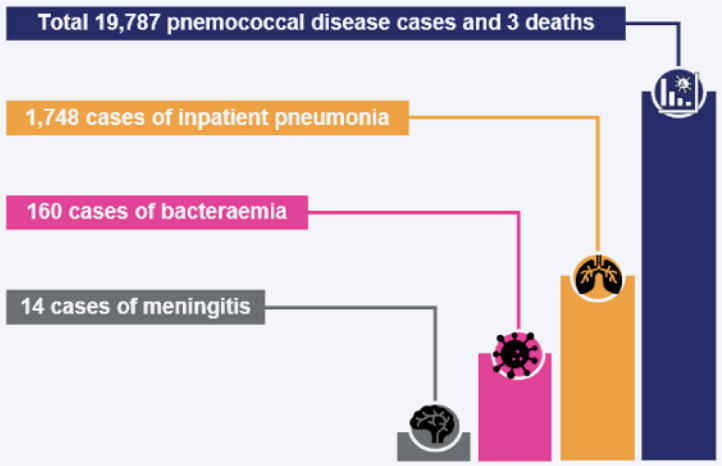


TABLE 5: Deterministic incremental results.

Model outcomes	PCV20 3+1 versus PCV13 2+1		
	Year 1	Year 2	Year 10
Total disease cases	-8,121	-19,787	-184,994
IPD	-79	-175	-1,343
Meningitis	*-7*	*-14*	*-109*
Bacteraemia	*-72*	*-160*	*-1,234*
Inpatient pneumonia	-710	-1,748	-16,452
Outpatient pneumonia	-617	-1,501	-13,711
OM	-6,715	-16,362	-153,488
Number of deaths due to disease	-2	-3	-30

The reported results are for children aged 0 – 17 only. Summed data (e.g., total cases) may not exactly match the sum of the breakdown due to rounded values (i.e., totals and breakdowns were rounded separately from decimals). Abbreviations: IPD, invasive pneumococcal disease; OM, otitis media; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine.

Compared to the current SoC (PCV13 2+1), PCV20 3+1 was estimated to prevent 184,994 cases over 10 years, including 1,343 cases of IPD, 16,452 cases of inpatient pneumonia, 13,711 cases of outpatient pneumonia, and 153,488 cases of OM, as well as 30 lives saved.

Within one year, maintaining the SoC (PCV13 2+1) was estimated to result in 8,121 cases of pneumococcal disease and two disease-related deaths that otherwise could have been prevented by PCV20 3+1. By Year 2, the forgone health benefits in terms of pneumococcal disease cases averted were projected to more than double at 19,787 cases that could have been prevented, due to the accrual of the indirect effects.

Scenario assessment results

PCV20 was estimated to prevent more pneumococcal disease cases and deaths versus PCV13 over 10 years in all tested scenarios (Table 6).

Scenarios including German incidence data for non-invasive disease inputs predicted a substantial increase in disease cases avoided compared with the base-case results, with small changes in number of disease-related deaths prevented. The scenario investigating 0% PCV20 vaccine effect for serotypes 3, 4, 9V, 23F, and 12F in the first year of life estimated a reduced public health benefit of PCV20 versus PCV13 compared with the base-case. However, PCV20 remained the strategy avoiding most disease cases and deaths.

Scenarios excluding all indirect effect and considering serotype replacement resulted in largest deviations from the base-case results. When only direct effects were assumed across all disease endpoints, the additional pneumococcal disease cases averted by PCV20 compared to PCV13 decreased by nearly fivefold, while the number of additional deaths prevented was roughly threefold lower than in the base case. Similarly, assumptions allowing for reduction in the distribution of newly covered PCV20 serotypes over time due to serotype replacement led to substantial attenuation of incremental health benefits relative to the base case, with approximately 90% reduction in cases averted and between 17% and 33% reduction in additional deaths avoided. Nevertheless, across all scenarios, PCV20 remained associated with the largest reduction in overall pneumococcal disease burden between the two vaccine strategies. Notably, the scenario that assessed PCV20 administered under a 2+1 schedule demonstrated the least deviation from the base-case results in pneumococcal disease cases prevented with PCV20 versus PCV13, suggesting that PCV20 implementation in either schedule could have similar impact.

Discussion

This study investigated the public health impact in the paediatric population (0-18 years of age) of implementing PCV20 3+1 into the Belgian paediatric NIP and evaluated the potential consequences of continuing to delay the implementation of PCV20. The findings of the deterministic analyses predicted that PCV20 implementation could result in substantial public health benefits over 10 years compared to maintaining PCV13. Additionally, the analysis demonstrated the short-term consequences of maintaining PCV13 in the NIP by estimating a

TABLE 6: Scenario assessment incremental results (over 10 years).

Model outcomes	PCV20 versus PCV13	
	Disease cases	Disease-related deaths
Deterministic results	-184,994	-30
1. Non-invasive disease incidence data from Germany (39-41).	-217,743	-33
2. 0% PCV20 vaccine effect for serotypes 3, 4, 9V, 23F, and 12F during first year of life.	-183,832	-30
3. Considering indirect effects for all ages, excluding the 45.6% of ≥65-year-olds assumed vaccinated (46)	-208,221	-1,154
4. 0% indirect effects for all ages.	-38,490	-9
5. ST replacement: 5% annual reduction.	-18,557	-25
6. ST replacement: 10% annual reduction.	-14,830	-20
7. PCV20 in 2+1 schedule (direct IPD vaccine effect of 88.7% for all vaccines) (23).	-184,158	-30

Abbreviations: IPD, invasive pneumococcal disease; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; ST, serotype.

substantial number of disease cases and deaths that otherwise could have been prevented if PCV20 were implemented. Postponing the rollout of PCV20 by 1 year could result in over 8,000 cases of potentially avoidable pneumococcal disease, with this number more than doubling after 2 years. These results highlighted that delaying the transition to PCV20 could result in a considerable, preventable pneumococcal disease burden, especially for non-invasive infections such as pneumonia and OM. Belgium recently experienced a record rise in IPD in winter 2024–2025, with over 95% of disease cases caused by vaccine-preventable serotypes, of which the six most common serotypes - 12F, 8, 3, 19A, 4, and 14 – are all covered by PCV20 (51). These findings, along with the results of this analysis, underscored the need to adopt higher-valent vaccines such as PCV20 in Belgium's paediatric NIP. Furthermore, the results of this study aligned with those of several European studies, such as Germany, Greece, the Netherlands, Spain, and the UK, as well as from other countries around the world, such as Canada, Argentina, Mexico, Japan, and South Korea, indicating health benefits of PCV20 versus PCV13 (8-11, 14, 15, 52-54).

Although IPD tends to cause more severe symptoms, pneumonia and OM are more prevalent manifestations of pneumococcal disease and represent the majority of disease burden in children (55). Pneumonia and OM in children can also reduce caregiver quality of life and increase societal burden due to productivity loss (56, 57). Because of their high incidence, pneumonia and OM drove overall disease impact in this analysis, which was also observed in other analyses comparing PCV20 to lower-valent vaccines (8, 10, 12, 15, 58-60). Data from clinical trials and observational studies demonstrate PCV7 and PCV13 effectively reduced OM and pneumonia cases and incidence in children under five, making these important outcomes when assessing the benefits of higher-valent vaccines (61). Consequently, the model predicted PCV20 will also significantly lower non-invasive disease burden, though real-world data on its effects are currently unavailable.

Limitations of this study should be considered when interpreting the findings. Although Belgian-specific data were prioritised as input data to reflect the local context, some proxy data were used when local inputs were unavailable. The model assumed that IPD serotype coverage was comparable to that of non-invasive diseases, such as pneumonia and OM, due to the lack of specific data. This assumption was not unique to this study and has been used in several previously published public health impact and economic evaluation studies of PCVs (8-12, 53, 54). Due to the absence of real-world effectiveness data for PCV20 at time of this study, proxy estimates from lower-valent vaccines (PCV7 and PCV13) were used to estimate direct and indirect effects. These estimates were not specific to Belgium but were derived from several studies conducted in other European countries, such as France and the UK, based on feasibility assessments of several aspects, such as sample size and reliability (23-25, 33-38). Furthermore, the model estimated PCV13 and PCV20's impact against all-cause non-invasive disease rather than pneumococcal outcomes. The direct effect of vaccines on pneumococcal pneumonia and OM is difficult to estimate as there are limited data to regarding the proportion of all-cause disease that is pneumococcal (62). Additionally, the model employed data from PCV7 clinical trials which demonstrated efficacy against all-cause non-invasive disease outcomes, rather than pneumococcal specific ones, therefore this modelling approach was deemed appropriate. The base case analysis assumed average vaccine effectiveness across serotypes and did not model serotype-specific vaccine effects, as published estimates of serotype-specific effectiveness are limited by low case numbers per serotype and there is an absence of real-world evidence for PCV20's effectiveness against the newly covered serotypes. This approach intended to mitigate uncertainty, though it may overestimate true effectiveness for individual serotypes. However, scenario analyses were conducted to test whether the model outcomes would change considering alternative vaccine effect assumptions. Despite demonstrating slightly lower public health benefit for PCV20, the overall findings from those scenarios aligned with the conclusion of the base case analysis.

An important source of uncertainty of this analysis related to the assumption of indirect effects. The analysis assumed that indirect effects associated with PCV20 would be comparable to those observed with PCV13; however, the clinical data for PCV20 is limited to immunogenicity and PCV20 impact data, particularly for the seven additional serotypes is not yet available. While the relationship between immunogenicity and indirect effects is complex and not fully predictable, historical experience with PCV10 and PCV13 has demonstrated indirect protection following vaccine introduction even when immunogenicity outcomes vary across serotypes (45). Furthermore, meta-analytic and real-world evidence indicated that vaccines such as PCV10 and PCV13 can produce robust indirect protection across vaccine serotypes, regardless of minor differences in immunogenicity (47, 63). To evaluate the sensitivity of the results to this assumption, a conservative scenario excluding indirect effects was tested. This scenario significantly reduced the additional health benefits associated with PCV20 compared to PCV13, yet the conclusions remained consistent with the base case, with PCV20 estimated to result in a greater reduction in disease burden.

The base case analysis assumed no serotype replacement, which may overestimate the effects of PCV13 and PCV20. While some replacement is expected, the extent of such replacement remains unclear and cannot be reliably estimated, therefore modelling

serotype replacement would introduce unnecessary uncertainty. Although, the base case assumed no replacement effect, scenario analyses explored the impact of serotype replacement. While the results of these scenarios confirmed PCV20 would have greater public health impact compared to PCV13, the estimated number of averted cases was substantially decreased in these analyses, highlighting the influence of serotype replacement on the magnitude of expected health benefits. Another limitation of this analysis is that vaccine uptake was based on relatively dated national estimates reported by Sciensano (2021), reflecting the complete schedule of 3 doses of PCV13 across Belgium. The absence of more recent data represented a limitation. Nevertheless, historical data indicated that national PCV uptake among Belgian paediatric population has remained consistently high, at around 93% - 94% between 2012 and 2021(64).

Conclusion

This study estimated that vaccinating infants with PCV20 3+1 could prevent substantially more pneumococcal disease cases and disease-related deaths among Belgian children aged 0–17 years in the short (1-2 years) and long (10 years) term compared with the current SoC (PCV13 2+1). These results underscore the need to accelerate implementation of PCV20 into the Belgian paediatric NIP to maximize public health gains in Belgian children.

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