Cost-utility analysis of 15-valent pneumococcal conjugate vaccine in the immunization of adults over 65 years of age in the Czech Republic

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Background

Unlike new drugs, vaccines are currently not routinely subject to Health Technology Assessment (HTA) evaluation when entering the national healthcare reimbursement system in the Czech Republic (CZ). However, HTA evaluation of any new intervention is critical to ensure efficient allocation of scarce healthcare system resources. Therefore, a new pilot project was recently launched by the Ministry of Health of the Czech Republic to investigate the possibility of incorporating HTA methods in the standard process of granting reimbursement from the healthcare system to new vaccines in the Czech Republic, similar to what is currently applied to regular drugs in CZ.

PCV15 by MSD is a new 15-valent pneumococcal conjugate vaccine. Several phase III clinical trials observing the immunogenicity of PCV15 suggested, that PCV15 might be effective in the prevention of pneumococcal disease (PD) in adults. Pneumococcal disease is caused by Streptococcus pneumoniae and can either lead to non-bacteremic pneumonia (NBPP), causing mucosal non-invasive infections (e.g. community acquired pneumonia, and other respiratory tract infections), or invasive pneumococcal disease (IPD), including bacterial meningitis, bacteremia, and septicemia.(1) S. *Pneumoniae* is a major cause of morbidity and mortality in adults worldwide (2) and is the underlying pathogen in 30-50% of NBPP cases. Vaccination is the only public health strategy proven to reduce the incidence of IPD and NBPP. Two types of pneumococcal vaccines are currently available and reimbursed to adults aged 65 years and older in CZ: pneumococcal polysaccharide vaccine 23 (PPSV23) and pneumococcal conjugate vaccine 13 (PCV13). Both vaccines have been proven effective in protecting against IPD and NBPP.(3) However, because PD can occur from over 90 different serotypes, constant development and increase of serotype protection within vaccines is needed. PCV15 by MSD is a new vaccine that creates an immune memory against 2 additional serotypes (22F and 33F) compared with PCV13; moreover, it may also be more effective when protecting against the most common serotype in the Czech Republic and one of the most common worldwide – serotype 3, according to PNEU-AGE study (4).

Objectives

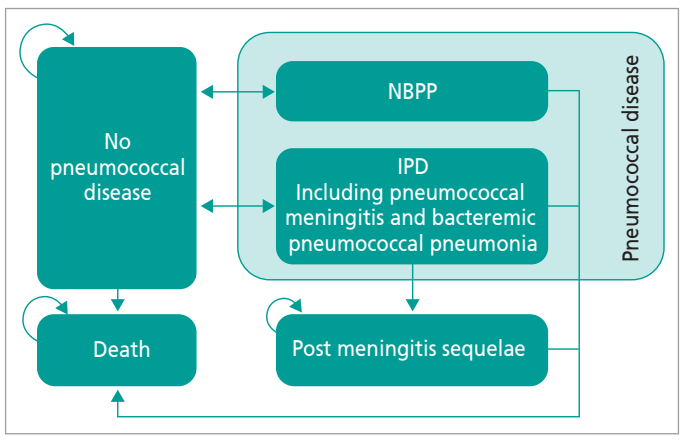
The objective of this study was to evaluate the cost-utility of PCV15 in combination with PPSV23 compared with PCV13 in a population comprising adults ≥65 years from the Czech health system perspective.

Methods

A published lifetime (i.e., 35-year) Markov cohort model with a one-year cycle length was used and adapted to project Quality-Adjusted Life-Years (QALYs) and the costs of pneumococcal vaccines for adults over 65 years of age in the Czech Republic. Costs and outcomes were discounted by 3%.(5) Costs were recalculated from CZK to € using exchange rate of 23.785 CZK/€. Deterministic (one-way, OWSA) and probabilistic sensitivity analyses (PSA; 1,000 iterations) with a Czech willingness-to-pay (WTP) threshold of €50,000/QALY (5) were conducted to determine the robustness of the findings. In both sensitivity analyses, the variables entering the model were varied within ± 20%.

The model health states are defined by the occurrence of pneumococcal disease and its type (IPD or NBPP), its consequences (meningitis, sepsis, pneumonia), and death (see **Figure 1**).

Figure 1. Markov Model Structure



Notes: IPD = invasive pneumococcal disease; NBPP = non-bacteremic pneumococcal pneumonia. Background mortality is applied to all health states in the model

The total population of the Czech Republic over 65 years of age enters the model (2,169,109 adults (6)). The pneumococcal vaccination coverage in the targeted population is assumed to be 24.5 % according to local sources.(7) Therefore, 531,432 adults are assumed to receive the vaccination.

Transitions between health states were determined based on the serotype-specific incidence of PD, the probability of PMS, and PD lethality. For the vaccinated cohort in the model (531,432 adults), serotype-specific incidence was reduced at a rate consistent with the expected vaccine efficacy. Although clinical trials have suggested better immune responses of PCV15 against serotype 3 than PCV13, there is no serological (OPA GMT or IgG GMC) surrogate of protection in adults. Because of this, it is unknown if the higher immune responses to ST3 with PCV15 as compared to PCV13 will translate into improved clinical efficacy. For this reason, the model conservatively assumes equal protection against the 13 shared serotypes (including serotype 3) for both vaccines which may underestimate it's the true benefits of PCV15.

The efficacy values against both IPD and NBPP are based on the literature. The only randomized controlled trial by Bonten et al., 2015 (8) reported efficacy for PCV13 of 75% against IPD and 45% against NBPP against all vaccine-covered serotypes. Given the similar efficacy assumption, the same values were assumed for PCV15 against all vaccine-covered serotypes. For PPSV23 serotypes, the efficacy of the vaccine against IPD was obtained from the systematic review and meta-analysis by Falkenhorst et al., 2017 (9) – **73% efficacy against IPD**, and for the efficacy of the vaccine against NBPP a prospective cohort study by Tanimoto et al., 2017 (10) – **33.5% efficacy against NBPP** was used. Against all other serotypes not covered by each vaccine, an efficacy of 0% is calculated.

The serotype distribution in the Czech population was derived from local data (see **Table 1**).

Table 1. Serotypes of IPD cases for the year 2021 in the Czech Republic (11)

Serotype	Number of cases among adults ≥65 years	Percentage of serotype	
4	5	3.57%	13 serotypes shared by PCV13 and PCV15
6B	3	2.14%	
9V	0	0.00%	
14	6	4.29%	
18C	0	0.00%	
19F	3	2.14%	
23F	0	0.00%	
1	0	0.00%	
5	0	0.00%	
7F	0	0.00%	
3	**24**	**17.14%**	
6A	2	1.43%	
19A	13	9.29%	
2	0	0.00%	
8	15	10.71%	
9N	13	9.29%	
10A	2	1.43%	
11A	3	2.14%	
12F	1	0.71%	
15B	0	0.00%	
17F	1	0.71%	
20	2	1.43%	2 additional serotypes of PCV15
22F	**9**	**6.43%**	
33F	**0**	**0.00%**	
6C	14	10.00%	
7C	1	0.71%	
9A	0	0.00%	
11C	1	0.71%	
15A	3	2.14%	
16F	0	0.00%	
18F/A/B/C	0	0.00%	
23A	3	2.14%	
23B	0	0.00%	
28F	1	0.71%	
31	2	1.43%	
34	0	0.00%	
35A	1	0.71%	
35B	1	0.71%	
35F	3	2.14%	
36	0	0.00%	
37	0	0.00%	
Not identified	8	5.71%	
Total	**140**	**100.00%**	

The costs of vaccines were based on the Czech valid list of reimbursed medicinal products (12) (see **Table 2**). Each dose of vaccine is also associated with a one-off administration cost which is €12.19 according to the Ministry of Health's list of health services (13).

Table 2. Vaccine costs

Vaccine	Cost per dose (EUR)
PCV15	€71
PPSV23	€26
PCV13	€62
PCV15+PPSV23	€97

Medical costs related to each health state were based on the costs of CZ-DRG groups published by the Institute of Health Information and Statistics of the Czech Republic or calculated based on Czech experts, which defined the consumed resource use (see **Table 3**).

Table 3. Healthcare costs

Health State	CZ-DRG code	DRG name	Costs per case (EUR)
IPD	18-K01	Sepsis	€4,801
NBPP inpatient	04-K02	Lung infection	€2,665
NBPP outpatient	–	Not covered by CZ-DRG, costs are based on expert opinion only	€399
Meningitis	01-K02-01 01-K02-02	Bacterial neuroinfection or herpetic meningoencephalitis	€6,085
PMS	–	Not covered by CZ-DRG, costs are based on expert opinion only	€4,204

Baseline utilities for the "No pneumococcal disease" health state were calculated by age based on the Ara and Brazier 2010 (14) equation for general population utilities. Utility decrements based on the literature were applied to patients in other PD-related health states.

Table 4. Utility decrements

Health state	Utility decrement per day	Reference
IPD	0,009	Stoecker et al., 2018 (15)
NBPP outpatient	0,004	Stoecker et al., 2018 (15)
NBPP inpatient	0,006	Stoecker et al., 2018 (15)
Meningitis	0,023	Bennett et al., 2000(16)
PMS	0.690*	des Portes, 2009(17)

*For post meningitis sequelae (PMS), the value is not a decrement, but a utility value of 0.69 is applied for all patients in the PMS health state

Results

Over a lifetime horizon, PCV15+PPSV23 provides additional 659 QALYs (12,680,929 vs. 12,680,270) per Czech population of adults aged ≥65 years (2,169,109 adults of which 531,432 vaccinated) at an additional total cost of €19,676,801 (€348,783,253 vs. €329,106,452) (per the same population) compared with PCV13, yielding an incremental cost-effectiveness ratio of €29,859/QALY gained (see **Table 5**).

Table 5. Cost-utility analysis results

	PCV15 + PPSV23	PCV13	Increment
Costs per population	€348,783,253	€329,106,452	€19,676,801
LYG per population	22,919,532	22,918,151	1,381
QALY per population	12,680,929	12,680,270	659
ICER/LYG	€14,252/LYG		
ICER/QALY	**€29,859/QALY**		

Probabilistic sensitivity analysis demonstrated that the probability of PCV15+PPSV23 being cost-effective is 100% at the WTP threshold (see **Figure 2** and **Figure 3**), the average probabilistic ICER (€29,904/QALY) is very close to base-case deterministic ICER. OWSA confirmed the robustness of the results (see **Figure 4**).

Figure 2. Probabilistic sensitivity analysis

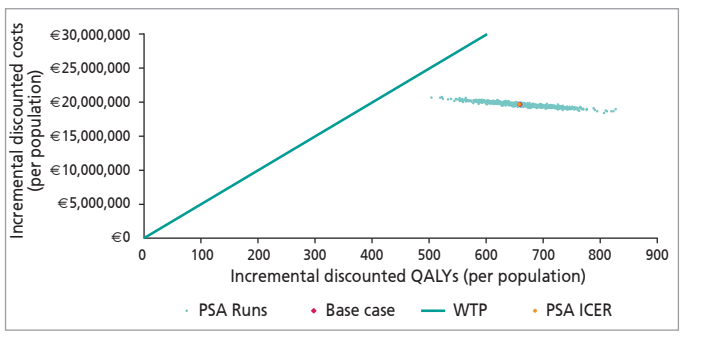


Figure 3. Cost-effectiveness acceptability curves

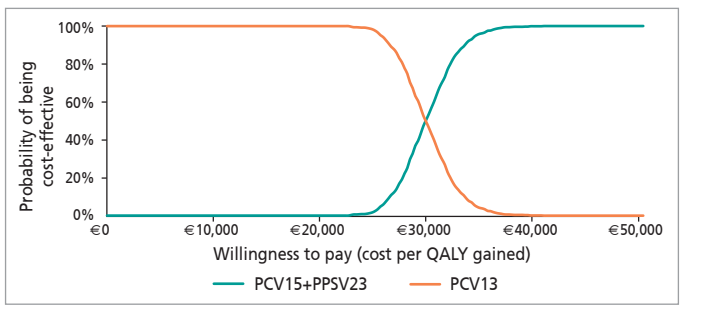
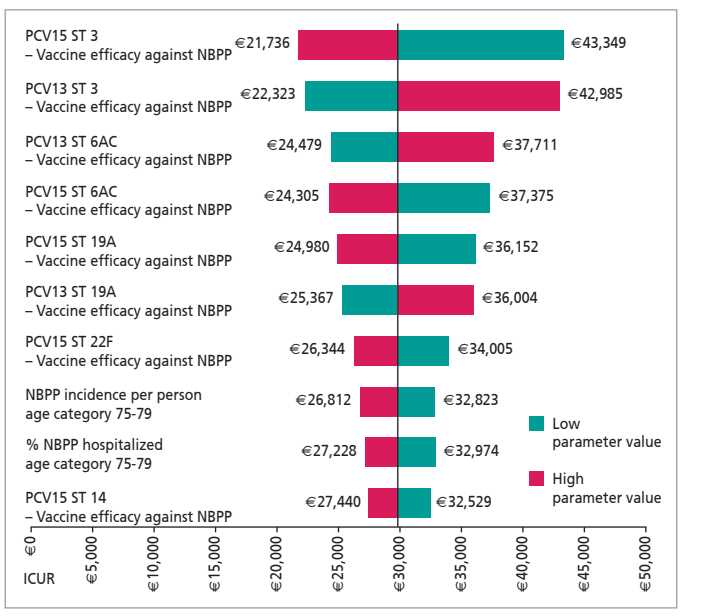


Figure 4. One-way sensitivity analysis



Discussion

The key advantages of the analysis are the use of accurate local data on the current percentage of each serotype in the Czech population and the head-to-head studies with the comparator forming the evidence base for the analysis.

A limitation of this analysis may be the lack of data on the local incidence of PDs; however, the applicability of the model results to the Czech population is assumed to be ensured by using local serotype distribution data. Another limitation is the lack of long-term data on patient protection against the disease in real clinical practice, mainly in the context of comparative effectiveness and the correlation between the clinical efficacy observed in phase 3 clinical trials (immunogenicity) and the actual protection against the disease (the percentage by which the incidence of PDs in vaccinated patients is reduced). The issue of comparative effectiveness is conservatively addressed in the model by assuming equal efficacy of PCV15 and PCV13 against all vaccinated serotypes, even though clinical data suggested a statistically significantly higher immune responses of PCV15 for serotype 3.

Conclusion

Based on the results of the cost-utility analysis, PCV15+PPSV23 represents a cost-effective vaccination strategy for adults aged ≥65 years in the Czech Republic compared to PCV13. This analysis is part of a Czech pilot project requested by the Ministry of Health to test and examine of feasibility of the implementation of HTA for vaccines because vaccines are currently not subject to HTA in the Czech Republic.

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