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Cost-Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine in Switzerland

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Abstract

The 7-valent pneumococcal conjugate vaccine (PCV7) has been shown to be highly cost-effective. The 13-valent pneumococcal conjugate vaccine (PCV13) offers seroprotection against six additional serotypes. A decision-analytic model was constructed to estimate direct medical costs and clinical effectiveness of PCV13 vaccination on invasive pneumococcal disease (IPD), pneumonia, and otitis media relative to PCV7 vaccination. The option with an one-dose catch-up vaccination in children of 15-59 months was also considered. Assuming 83% vaccination coverage and considering indirect effects, 1'808 IPD, 5'558 pneumonia and 74'136 otitis media cases could be eliminated from the entire population during a 10-year modelling period. The PCV13 vaccination programme would lead to additional costs (+€26.2 Mio), but saved medical costs of -€77.1 Mio due to cases averted and deaths avoided, overcompensate these costs (total cost savings -€50.9 Mio). The national immunization programmes with PCV13 can be assumed cost saving when compared with the current vaccine PCV7 in Switzerland.

Key words: cost-effectiveness, pneumococcal, vaccination.

Running head: Cost-effectiveness of PCV13 vaccination

I. Background

Streptococcus pneumoniae (pneumococcus) is a bacterial pathogen causing about 1-2 million death among children worldwide¹⁻³. Generally, the pathogen colonises in the upper respiratory tract causing pneumonia, bacteremia, meningitis and otitis media which are associated with considerable numbers of cases of morbidity and mortality⁴. Invasive pneumococcal disease (IPD) like bacteremia, bacteremic pneumonia or meningitis is most prevalent among children, the immunocompromised and the elderly⁵. The transmission of pneumococcus requires direct contact with contaminated respiratory secretions between individuals⁶. However, the underlining treatment of the infections is often complicated due to resistance of the pathogen to several classes of antibiotics⁷.

The 7-valent protein conjugated pneumococcal vaccine (PCV7, Prevenar®, Pfizer) was shown to be highly efficacious in preventing invasive pneumococcal infections, pneumonia and otitis media in infants as well as in young children⁸⁻¹⁰. The 13-valent vaccine (PCV13, Prevenar 13®, Pfizer) includes six additional serotypes, including serotype 19A which is associated with increased disease rates and hospital admission after the introduction of PCV7¹¹. The American Academy of Pediatrics Committee on Infectious Diseases postulated that PCV7 should be replaced by PCV13, and used in health and children at-risk¹²

Given that pneumococcal vaccines can decline nasopharyngeal carriage of vaccine strains in vaccinated children, the rate of pneumococcal disease in non-immunized individuals can be reduced, designated as indirect or herd effect¹³. Cost-effectiveness studies take generally both the direct and indirect effect of immunisation into account to provide a more comprehensive evaluation of the vaccine¹⁴.

It was shown that pneumococcal conjugate immunisation programmes can reduce mortality and long term neurologic impairment at a reasonable cost-effectiveness ratio for Swiss infants^{15, 16}. The pneumococcal vaccination schedule is a 2+1 schedule in Switzerland¹⁷. In 2010, PCV13 has been approved by the Swiss Agency for Therapeutic Products (Swissmedic)¹⁸.

The objective of the present study is to assess the potential health benefits and costs associated with pneumococcal vaccination strategies for the entire population. A decision-analytic model was used to simulate a Swiss birth cohort during a ten-year horizon.

II. Methods

2.1. Overview of the model

The aim of this model was to assess the clinical and economic consequences in Switzerland, in particular, of the 13-valent conjugated pneumococcal vaccine (PCV13), with or without serotype catch-up vaccination, versus the 7-valent vaccine (PCV7). A decision analysis model was applied to an annual birth cohort of 77'019 children¹⁹⁻²¹(Figure 1).

The model considered various disease states including no disease, IPD (i.e. bacteremia or meningitis), inpatient and outpatient pneumonia and otitis media (complex and simple). For each disease state, the percentage of disease covered by the vaccine's serotype (for serotype covered disease), the vaccine coverage rate and the direct and indirect effect (herd effect) of the vaccine were applied to the entire population within each age-group. Direct and indirect effect of the vaccine was applied to vaccinated and unvaccinated

individuals, respectively. Within each health states corresponding costs (direct medical costs per episode and vaccine acquisition and administration, where applicable) and utilities were assessed in each vaccination strategy.

Effectiveness was determined as quality-adjusted life-years (QALYs) and life year gained (LYG). Cumulative direct costs associated with each vaccination programme were estimated. Incremental cost-effectiveness ratios (ICERs) were planned to be measured if applicable.

Demographic information on the Swiss patient population, data on disease incidence and fatality rates, direct costs, vaccine properties and utility inputs were determined to estimate the cost-effectiveness of the scenarios described above. Costs and effects were discounted at 3%. Costs are shown in Euros (1 Swiss Francs (CHF) = 0.82 Euro (EUR), February 2012). The model time horizon was ten years.

2.2. Patient population studied

The model was constructed with a hypothetical cohort of the general population in Switzerland. Total population, percentage of the population in the newborn cohort (below the age of 1 year) and the proportion of the vaccinated population were assessed from the Swiss perspective²¹. In Switzerland, the pneumococcal vaccination coverage rate in children below 2 years of age is currently 83%. The model assumed a constant coverage rate throughout the modelling period.

The model distinguished between different age groups (0-2, 2-4, 5-17, 18-34, 35-49, 50-64, 65+ years) and the incidence of disease in those age groups for Switzerland (Table 1). Due to different event probabilities, age-stratification was crucial to our analysis. Children below the age of 5 were eligible for vaccination. The adult population in our

model was assumed to be unvaccinated. Life expectancy in Switzerland is 79.7 and 84.4 years for males and females, respectively²².

2.3. Strategies compared

Base-case

In the base-case, the model considered two strategies: 7-valent vaccine (PCV7) versus 13-valent conjugated pneumococcal vaccine (PCV13). In Switzerland, pneumococcal vaccination schedule is a 2+1 schedule (2 primary vaccination at age of 2 month and 4 month and one booster dose at age of 12 month)¹⁷. Due to low clinical relevance, the strategy with no vaccination was not taken into account.

Catch-up

An additional analysis considered PCV13 versus PCV13 with catch-up vaccination. The PCV13 serotype catch-up strategy intended to administer one additional dose of PCV13 to children who completed their PCV7 series. This option assumed that children aged 15-59 months will accelerate the direct and indirect effect due to one dose of PCV13 by 1 year²³. The vaccination rate of the catch-up strategy was assumed at 15%.

2.4. Disease stages

The model included six different health states: no disease, IPD (i.e. IPD that are pneumococcal meningitis or pneumococcal bacteremia), inpatient pneumonia, outpatient pneumonia, simple and complex all-cause otitis media (Figure 1). IPD cases are clinically defined by isolating *Streptococcus pneumoniae* from a normally sterile body site²⁴. In our case, IPD was confirmed by clinical syndromes and classified as pneumonia,

bacteraemia, meningitis or arthritis²⁵. The latter symptom was not considered in our model.

Patients contracting meningitis were prone to develop sequelae such as neurological impairment or hearing loss (mutually exclusive). These conditions were assumed to increase costs of health care service and reduce a patient's lifetime utility by decrementing the baseline utility and persisting for the remainder life. Patients contracting bacteremia, meningitis, and pneumonia were assumed to have an increased risk of death due to illness specific conditions. The remainder were supposed to recover from the disease. All-cause mortality was estimated from the age distribution of the patient population and the conditional expected remaining life years by each age-group.

2.5. Clinical data source

Incidence of disease

Streptococcus pneumoniae can cause different diseases. The Incidence per age group for IPD (meningitis, bacteremia, pneumonia), hospitalised CAP and all-cause otitis media (derived from the Federal Office of Public Health Switzerland (FOPH) and the Institute for Infectious Diseases (IFIK) Berne, Switzerland²⁶. The numbers of cases (per 100'000 individuals) of each disease for the year 2007 or 2008 are presented in Table 1, respectively. Fatality rates classified by age group and disease were presented in Table 2. Complication rates were assessed from published literature²⁷. Neurologic impairment or hearing loss due to meningitis were assumed to occur in 7% or 13%, respectively²⁷.

Serotype coverage

The serotypes covered by PCV7 (4; 6B; 9V; 14; 18C; 19F; 23F) and PCV13 (1; 3; 4; 5; 6A; 6B; 7F; 9V; 14; 18C; 19A; 19F; 23F), respectively, were considered by disease and age class within the model. IPD was assumed to be serotype covered while pneumonia and otitis media was all-cause. Given that pneumonia and otitis media were from an all-cause perspective, the serotype coverage was implicitly taken into account for calculating vaccine effectiveness.

Serotype coverage was assessed from the database of the FOPH and the IFIK²⁶ (Table 3). The inputs of the PCV7 serotype coverage reflects the coverage of the time of its introduction²⁵ (reimbursement in Switzerland since August 2006). Serotype coverage of PCV13 was considered from the year 2008 to reveal the coverage in the selected era of the disease incidence.

Vaccine direct effect

Direct effectiveness is represented by the reduction in disease among vaccinated individuals. PCV13 effectiveness was calculated by taking into account both direct effectiveness from PCV7 and the serotype producing systemic disease in Switzerland²⁶. Vaccine effectiveness is defined as the proportion of vaccinated population that exhibits immunity to vaccine covered serotype of pneumococcal bacteria.

Effectiveness against covered types indicates the effectiveness of the vaccine against the serotypes included in the vaccine. For the heptavalent vaccine, direct efficacy among children below one year of age was estimated at 72.3%, 6.0%, 6.0%, and 7.0% for IPD, inpatient pneumonia, outpatient pneumonia and all-cause otitis media, respectively^{28, 29}.

Effectiveness against IPD for covered serotypes was assumed equal for PCV7 and

PCV13^{23, 28}. Non-IPD effectiveness against covered types was expected to be the same for PCV7 and PCV13. Hence, the effect for non-IPD was calculated based on direct PCV7 effect and the increase in the additional serotype coverage provided by PCV13 as observed in the Swiss population ((PCV13 effectiveness = effectiveness of PCV7 * (1 + (serotype coverage of PCV13 / serotype coverage of PCV7))). Correspondingly, direct effects of PCV13 was calculated for children below 2 years of age (Table 4).

It was assumed that the vaccine effectiveness (cases avoided) among children <12 months was reduced by 1/3 to reflect children <2 months that were not vaccinated and children 2-<4 months who may not mount an immune response. Direct effect was assumed to decline by 3% annually in the first three years of life (waining of 9% in total)^{30, 31}. Hence 91% of the original vaccine efficacy was applied for children of the age group 3-5 years³⁰.

Vaccine indirect effect

The indirect or herd effect provides indirect protection to unvaccinated individuals given that vaccinated individuals are less likely to carry vaccine-type pneumococci^{32, 33}. The impact of acceleration of indirect effects is hard to determine, however we presumed herd effects of PCV7 for IPD and non-IPD (complex otitis media Sand hospitalised pneumonia) derived from published literature³⁴. PCV13 indirect effectiveness against covered types for non-IPD was assessed based on the indirect effectiveness of PCV7 and its proportional serotype coverage (Appendix 1, Table 3). In order to use a conservative approach, we divided the additional age-specific serotype adjustment by two.

The vaccine was assumed to have a direct effect in children below the age of five^{28, 29}, but decreased rates of disease incidence in individuals aged five years and above were

assumed to be due to indirect vaccine effects (Table 4, Appendix 1)¹⁰. The expected proportion of reduced disease cases in IPD and non-IPD stands for the indirect effectiveness of non-vaccinated individuals. After seven years of initial vaccination, the indirect effects reached a cumulative steady state of 100%.

2.6. Unit costs

Direct medical costs included vaccine related costs, physician time, medication, diagnostic tests consumed and hospitalization costs. Unit costs for vaccine administration, laboratory and diagnostic interventions derived from the official Swiss tariff book³⁵. Hospital case-based flat rates and day rates were based on Swiss Diagnosis Related Groups (DRGs)³⁶. Drug and vaccine costs were based on official Swiss pharmacy prices³⁷.³⁸ Health states with no disease were assumed to have no costs, besides the cost of the vaccine. Costs and quantity of diagnostics and therapeutic interventions were assessed on this basis for all disease outcomes assessed (Appendix 2). We did not include indirect costs to society as loss of income due to death or severe sequelae.

2.7. Medical resource use

Resource utilisation quantities for pneumococcal diseases were obtained from expert panel consultation and systematic literature research.

One meningitis episode was assumed to require radiology, computer tomography (CT) and magnet resonance imaging (MRI) of the cranium, hearing tests, lumbal puncture and culture. During a bacteremia episode, radiology, computer tomography (CT) and magnet resonance imaging (MRI) of the thorax, lumbal puncture and culture was presumed to be

needed. Diagnostic interventions for pneumonia and otitis media episode were CT, radiography and MRI of the thorax, depending on the complexity of the disease course. It was assumed that 20% of complex otitis media cases would require a ventilator tube replacement³⁹.

Length of hospital stay was based on data provided by the Swiss Federal Statistic Office (adults \geq 18 years) and expert opinion (children $<$ 18years)⁴⁰. Admission rates and average hospital stay are presented in Appendix 3. In all cases, blood tests and antipyretic / analgesic drugs were prescribed, hence those costs were not included in the model. The model took into account future medical costs of €820 (deafness) and €4'100 (disability) per year for children with sequelae from meningitis¹⁵.

2.8. Utilities

Preference-based measures of health related quality of life were available from the published literature^{15, 41-45}. Utilities are measured on a 0-1 scale where 1 corresponds to perfect health. Baseline utility for a healthy individual was 0.9⁴⁶. Per episode utility reduction for meningitis (0.0232)⁴¹, bacteremia (0.0079)⁴¹, simple (0.004)⁴⁵ and complex pneumonia (0.006)⁴⁵ as well as otitis media (0.005)⁴⁴ were used in the model. Hearing loss and disability were assumed to reduce a patient's lifetime utility by a factor of 0.8 and 0.6, respectively^{42, 43}. Utility values were supposed to be independent of age.

Total QALYs were determined by multiplying discounted average life expectancy with the health utility index of an individual in a certain health state. QALYs lost due to disease sequelae were subtracted from the QALYs of the entire population to obtain the total QALYs.

2.9. Sensitivity analysis

Deterministic sensitivity analyses (DSA) were performed to test the impact of parameter uncertainties on the number of pneumococcal cases avoided and according cost consequences. The following variables were included in the sensitivity analyses (DSA cases): vaccination coverage of PCV7, vaccination coverage of PCV13, incidence simple otitis media, direct effectiveness of PCV13 versus simple otitis media, waning of direct effectiveness, incidence of IPD, IPD direct effectiveness of PCV13, incidence of complex otitis media, indirect effectiveness of simple otitis media of PCV13, direct effectiveness of PCV13 versus complex otitis media. DSA in regard to costs were performed with the variables as follows: incidence of IPD, indirect IPD effectiveness of PCV13, medical costs of bacteremia, costs of 1 vaccine dose, annual medical cost of disability, proportion of IPD cases that are meningitis, medical costs of simple otitis media, incidence of simple otitis media, medical costs of meningitis and incidence of complex otitis media. All variables were varied within $\pm 20\%$.

III. Results

3.1. Base-case result (PCV13 vs PCV7)

The base-case measured the impact of PCV13 as the reduction in the burden of disease and associated costs. With 83% vaccination coverage, a total of 660'563 children would be vaccinated during a ten-year period (yearly average: 66'056).

Epidemiologic result

The direct effect of the vaccine accounts for a considerable reduction in disease cases in the PCV13 vaccine programme. The proportion of IPD and non-IPD cases avoided in non-vaccinated individuals (age 5 years and above) can be attributed to herd immunity (Table 4).

The model assumed that, in addition to the benefit of PCV7, PCV13 would reduce the number of pneumococcal meningitis and bacteraemia (IPD) by further 1'808 cases. Furthermore, it was estimated that 4'654 and 904 hospitalized and non-hospitalized pneumonia cases could be averted in the entire Swiss population, respectively. The incremental number of all-cause otitis media cases for the comparator strategy relative to the baseline strategy includes the cumulative number of the young population below five years of age over the entire modelling period. With the implementation of PCV13, it is estimated that additional 215 IPD related fatalities could be avoided (Table 5).

Costs

The cost estimates per disease episode differed considerably. In fact, highest costs per episode were found for complex diseases like meningitis, bacteriemia, hospitalised pneumonia and complex otitis media with €10'713, €4'887, €4'286 and €1'793, respectively. Less complex diseases as e.g. Simple otitis media or non-hospitalised pneumonia resulted in about €140 and €295 per episode, respectively (Appendix 4).

The vaccination programme with PCV13 would require an additional investment of about €26.2 Mio assuming a constant vaccine coverage of 83%. On the other hand, PCV13 resulted in costs savings of €18.3 Mio, €34.0 Mio and € 25.6 Mio attributed to IPD, pneumonia and all-cause otitis media, respectively. Accordingly, direct medical costs of

about -€ 96.9 Mio could be saved by PCV13, leading to total cost savings of -€77.1 Mio in Switzerland (Table 5).

Cost-effectiveness

Base-case

Across the entire Swiss population, the PCV13 vaccination programme saved 23'242 life-years and gained 18'172 QALYs over a ten-year period. This translates into a cost-saving situation of -€77 per child vaccinated (Table 5). If no herd protection would be considered, the cost-effectiveness ratio would increase to EUR 16'342 per QALY gained with costs of EUR 10 per child vaccinated (LYG=0). *Catch-up programme*

In the catch-up strategy, 42'360 children would receive catch-up vaccination (up to 59 months of age). The model predicts that the implementation of a catch-up programme for children aged 12-59 months in Switzerland would lead to direct protection combined with accelerated indirect impact resulting in 196 IPD and 3'592 non-IPD cases avoided and 275 averted deaths. In fact, the catch-up programme gained 1'608 QALYs and 2'182 life years. The additional vaccine course would cost additional €+4.0 Mio, whereas averted disease cases and disease related fatalities yielded in reduced medical costs of -€9.4 Mio. Accordingly, the cost-effectiveness ratio resulted in a cost-saving situation (Table 5). By considering only children below the age of 2 years in the catch-up programme, the situation would translate into cost-savings of €1'189 per child vaccinated.

3.2. Sensitivity analyses

By the help of sensitivity analyses, the robustness of the model base-case could be assessed. For the deterministic sensitivity analyses, cost and effectiveness were varied to

the extremes of $\pm 20\%$. The strongest impact on the number of avoided pneumococcal cases found in the base-case was obtained by varying the vaccination coverage and the incidence of simple all-cause otitis media. On the other hand, the base-case result regarding the costs was mainly influenced by the medical costs of hospitalised pneumonia, the incidence of hospitalised pneumonia as well as PCV7 indirect effect of averting hospitalised pneumonia (Figure 2).

IV. Discussion and conclusion

In our analysis, we assessed the prospective cost-effectiveness of a vaccination programme with PCV13 compared to the current available PCV7. The model included the impact of direct and indirect vaccine effects among the entire Swiss population. Although the introduction of PCV13 would increase the expenses for the pneumococcal vaccine program itself when compared to PCV7, the reduced medical costs due to avoided cases would overcompensate these costs over a ten year period. PCV13 vaccination would result in a cost-saving situation. The additional option of a catch-up vaccine programme indicated a favourable cost-effectiveness ratio when compared to the normal PCV13 vaccination schedule. Neither variation of cost- nor effectiveness input parameters did influence the model base-case results.

Rozenbaum and colleagues have recently presented a health economic evaluation with an unfavourable cost-effectiveness ratio for PCV7 in Dutch infants when net indirect effects (herd protection minus serotype replacement) were omitted (both for the 2+1 and 3+1 immunisation schedule)⁴⁷. The authors concluded that PCV7 does not provide enough protection with the serotypes included and hence does not lead to a health economic favourable result. However, by considering PCV13 vaccination with a three dose

schedule (2+1), the achieved cost-effectiveness ratio would be much favourable (€33'481/QALY compared to no vaccination). The better net health benefits of PCV13 can be mainly attributed to better herd immunity and reduced serotype replacement.

The major limiting factor was the data source. Although we tried to identify the most relevant and appropriate data, our model represents a simplification of the real-life disease outcome. For example, we did not take into account infections like endocarditis, arthritis, osteomyelitis, sinusitis or peritonitis, which might be linked to pneumococcal infections, especially among the adult population. Furthermore, most input parameters in regard to disease transmission came from various sources outside Switzerland, due to the lack of Swiss numbers. In addition, direct and indirect effects of PCV13 are yet not to be studied in the Swiss population. Hence, the data were calculated based on effects observed with PCV7 and the increase in serotype coverage of PCV13 compared to the seven-valent vaccine. This approach was also used in other studies^{48, 49}. Consequently, extensive sensitivity analyses have been performed to assess the robustness of the input parameters on the model's base-case result. We recognise that altered variable assumptions might have resulted in altered model results, but did not affect the conclusion of the analysis.

It may be argued that the cost-effectiveness ratio is indirectly driven by the applied indirect effects of the vaccine³². However, it remains unclear, if the herd immunity of PCV13 which was based on information derived from PCV7, is applicable to the serotypes covered. In our base-case analysis, we have taken into account herd protection of the unvaccinated individuals resulting in a reduction of the mortality rate of 2'886. In a sub-analysis, we have run the model omitting the indirect effect of the vaccination.

Nevertheless, the outcome of this analysis was still cost-saving. This underlines the work of Isaacman et al who investigated in a review whether indirect effects impacts the cost-effectiveness results¹⁴. The review come to the conclusion that indirect effects impact the cost-effectiveness considerable, and future models should include herd immunity when assessing the health economic impact of pneumococcal vaccines.

Due to the growing number of new vaccines, health economic models on immunisation programmes are more and more important to inform decision makers on health policies⁴⁷. Several studies have shown that PCV7 can be assumed cost-effective or even cost-saving, both in the Swiss¹⁵ and non-Swiss setting^{27, 30, 50-52}. It can be expected, that PCV13 may enhance the overall direct effect of the vaccination and offers positive herd protection in the non-vaccinated population.

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Figure legend

Figure 1. Decision analytic model structure

Figures 2 Deterministic Sensitivity Analyses (variables varied by $\pm 20\%$)

a) Effectiveness

b) Costs (Euro)

Table 1. Current annual incidence of IPD, pneumonia and all cause otitis media per age group (cases per 100'000 person-years, 2007/08)

	IPD*	IPD that are meningitis	IPD with pneumonia	CAP all*	CAP inpatient	CAP outpatient	all-cause otitis media** all	all-cause otitis media complex	all-cause otitis media simple
year	2008	2008	2008	2007	2007	2007	2007	2007	2007
age groups									
<12 months	32	33%	21%	280	42	238	15379	1538	13841
12-23 months	8	33%	33%	408	61	347	21539	2154	19385
24-35 months	12	0%	78%	328	49	278	14909	1491	13418
36-47 months	11	0%	63%	273	41	232	14802	1480	13322
48-59 months	13	0%	30%	231	35	196	14726	1473	13254
5-17 years	3	19%	66%	70	11	60	-	-	-
18-34 years	3	5%	59%	42	6	36	-	-	-
35-49 years	8	10%	65%	71	11	60	-	-	-
50-64 years	14.	7%	65%	167	25	142	-	-	-
65+ years	44	5%	70%	810	121	688	-	-	-

: CAP, community acquired pneumonia; IPD, invasive pneumococcal disease.

*it is assumed that 15% of CAP cases are hospitalized

**it is assumed that 10% of AOM are moderate to severe cases

Table 2. Fatality rates

	IPD all	Meningitis	Sepsis	Pneumonia all	CAP (2007)
Unit	(%)	(%)	(%)	(%)	(%)
Notes	Proportion of deaths per cases of IPD	Proportion of deaths with meningitis per IPD cases with meningitis	Proportion of deaths with sepsis per IPD cases with sepsis	Proportion of deaths with pneumonia per IPD cases with pneumonia*	Death of CAP was assumed to be all inpatient cases
age groups					
<12 to 59 months	0	0	0	0	0
5-17 years	0	0	0	0	0.17
18-34 years	0	0	0	0	0.76
35-49 years	5.3	0	10.0	4.0	2.71
50-64 years	8.3	28.6	13.4	6.0	11.43
65+ years	15.0	26.9	24.6	13.2	84.93

CAP, community acquired pneumonia; IPD, invasive pneumococcal disease.

*Hospitalization status of patients with pneumonia is not reported and therefore not known

NB: Multimanifestations are possible: one case may be counted to death with meningitis, with sepsis and with pneumonia

Table 3. 7-valent and 13-valent vaccine serotype coverage against all diseases (2006 / 2008)

Age group	PCV7*(2006)	Ref	PCV13**(2008)	Ref
<12 months	60.4%	²⁵	85.7%	²⁶
12-23 months	60.4%		100.0%	
24-35 months	53.6%		100.0%	
36-47 months	53.6%		100.0%	
48-59 months	53.6%		100.0%	
5-17 years	34.4%		89.3%	
18-34 years	42.8%		74.1%	
35-49 years	42.8%		69.1%	
50-64 years	42.8%		70.7%	
65+ years	38.2%		72.8%	

*Serotypes: 4; 6B; 9V; 14; 18C; 19F; 23F

**Serotypes: 1; 3; 4; 5; 6A; 6B; 7F; 9V; 14; 18C; 19A; 19F; 23F

NB: Cross-protection was not considered

Table 4. Direct and indirect effect due to PCV13

<i>Direct effect</i> ^{25, 26, 29*}					
	IPD	Pneumonia		Otitis Media	
age groups		Hospitalized	Non-hospitalized	Complex	Simple
<12 months**	41%	9%	9%	10%	10%
12-23 months	75%	16%	16%	19%	19%
Catch-up vaccination					
24- months	73%	17%	17%	10%	10%
36-47 months	70	17%	17%	5%	5%
48-59 months	59	17%	17%	5%	5%
<i>Indirect effect</i> ^{25, 26, 34} (Reduction in disease not attributable to direct effect)***					
	IPD	Hospitalized pneumonia		Complex otitis media	
<12 months**	48%	33%		22%	
12-23 months	56%	42%		27%	
24-35 months	43%	37%		0%	
				Catch-up: 29%	
36-47 months	43%	37%		0%	
				Catch-up: 29%	
48-59 months	41%	54%		0%	
				Catch-up: 29%	
5-17 yrs	37%	57%			
18-34 yrs	32%	25%			
35-49 yrs	30%	23%			
50-64 yrs	27%	22%			
65+ yrs	14%	24%			

IPD, invasive pneumococcal disease.

* non-IPD direct effect PCV13 = indirect effect PCV7 * (1 + ((serotype coverage of PCV13 / serotype coverage of PCV7)).

** It was assumed that the vaccine efficacy among children <12 months is reduced by 1/3 to reflect children <2 months that are not vaccinated and children 2-<4 months who may not mount an immune response.

***non-IPD indirect effect PCV13 = indirect effect PCV7 * (1 + ((serotype coverage of PCV13 / serotype coverage of PCV7)/2)).

Table 5. Base case and catch-up: cost-effectiveness results

	PCV13 versus PCV7	Catch-up program
Difference in direct costs (EUR)	-77.1 Mio	-9.4 Mio
Difference in vaccination costs (EUR)	+26.2 Mio	+4.0 Mio
Life years gained	23'242	2'182
QALYs gained	18'172	1'608
Cases avoided		
IPD	1'808	196
Hospitalized pneumonia	4'654	535
Non-hospitalized pneumonia	904	39
Complex all-cause otitis media	11'590	1'513
Simple all-cause otitis media	62'546	1'505
Death avoided		
IPD	215	25
Hospitalized pneumonia	2'125	250
Cost-effectiveness results		
Cost (EUR) per LYG	Cost-saving	Cost-saving
Cost (EUR) per QALY	Cost-saving	Cost-saving
Cost (EUR) per vaccinated child	-77	-222

IPD, invasive pneumococcal disease; QALY, quality adjusted life years, LYG, life year gained

NB: no deaths in 0-17 years old individuals

References

1. Berkley JA, Lowe BS, Mwangi I, Williams T, Bauni E, Mwarumba S, Ngetsa C, Slack MP, Njenga S, Hart CA, Maitland K, English M, Marsh K, Scott JA. Bacteremia among children admitted to a rural hospital in Kenya. *The New England journal of medicine* 2005; 352:39-47.
2. Bogaert D, De Groot R, Hermans PW. *Streptococcus pneumoniae* colonisation: the key to pneumococcal disease. *The Lancet infectious diseases* 2004; 4:144-54.
3. O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, Lee E, Mulholland K, Levine OS, Cherian T. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet* 2009; 374:893-902.
4. Feldman C, Anderson R. New insights into pneumococcal disease. *Respirology (Carlton, Vic)* 2009; 14:167-79.
5. Robinson KA, Baughman W, Rothrock G, Barrett NL, Pass M, Lexau C, Damaske B, Stefonek K, Barnes B, Patterson J, Zell ER, Schuchat A, Whitney CG. Epidemiology of invasive *Streptococcus pneumoniae* infections in the United States, 1995-1998: Opportunities for prevention in the conjugate vaccine era. *Jama* 2001; 285:1729-35.
6. van der Poll T, Opal SM. Pathogenesis, treatment, and prevention of pneumococcal pneumonia. *Lancet* 2009; 374:1543-56.
7. Feldman C, Anderson R. Controversies in the treatment of pneumococcal community-acquired pneumonia. *Future microbiology* 2006; 1:271-81.
8. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *The New England journal of medicine* 2003; 349:1341-8.
9. Musher DM. Pneumococcal vaccine--direct and indirect ("herd") effects. *The New England journal of medicine* 2006; 354:1522-4.
10. Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, Reingold A, Cieslak PR, Pilishvili T, Jackson D, Facklam RR, Jorgensen JH, Schuchat A. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *The New England journal of medicine* 2003; 348:1737-46.
11. Hausdorff WP, Feikin DR, Klugman KP. Epidemiological differences among pneumococcal serotypes. *The Lancet infectious diseases* 2005; 5:83-93.
12. Recommendations for the prevention of *Streptococcus pneumoniae* infections in infants and children: use of 13-valent pneumococcal conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23). *Pediatrics*; 126:186-90.
13. O'Brien KL, Dagan R. The potential indirect effect of conjugate pneumococcal vaccines. *Vaccine* 2003; 21:1815-25.
14. Isaacman DJ, Strutton DR, Kalpas EA, Horowicz-Mehler N, Stern LS, Casciano R, Ciuryla V. The impact of indirect (herd) protection on the cost-effectiveness of pneumococcal conjugate vaccine. *Clinical therapeutics* 2008; 30:341-57.
15. Ess SM, Schaad UB, Gervais A, Pinosch S, Szucs TD. Cost-effectiveness of a pneumococcal conjugate immunisation program for infants in Switzerland. *Vaccine* 2003; 21:3273-81.

16. Ruedin HJ, Ess S, Zimmermann HP, Szucs T. Invasive meningococcal and pneumococcal disease in Switzerland: cost-utility analysis of different vaccine strategies. *Vaccine* 2003; 21:4145-52.
17. EKIF. Eidgenössische Kommission für Impfungen - Pneumokokken Fact Sheet. 2006.
18. Documed. Prevenar® 13. 2010.
19. FSO. Federal Statistical Office: Bevölkerungsbewegung – Indikatoren Geburten und Fruchtbarkeit. 2008.
20. FSO. Federal Statistical Office: Todesfälle, Sterblichkeit und Lebenserwartung 2008.
21. FSO. Federal Statistical Office: Erhebungen, Quellen - Statistik des jährlichen Bevölkerungsstandes (ESPOP). 2008.
22. BFS. Federal Statistical Office: Todesfälle, Sterblichkeit und Lebenserwartung 2008.
23. Moore M. The Center's for Disease Control and Prevention Active Bacterial Core Surveillance (ABCs) program. 2009.
24. CDC. Case Definition Invasive Pneumococcal Disease, *Streptococcus pneumoniae*, invasive disease, Laboratory criteria for diagnosis. http://www.cdc.gov/osels/ph_surveillance/nndss/casedef/IPD_current.htm (), 2010
25. BAG. Bundesamt für Gesundheit - Pneumokokkenerkrankungen 2006. Bulletin 47 2007.
26. FOPH. Federal Office of Public Health FOPH - Pneumokokken-Erkrankungen.
27. Ray GT, Whitney CG, Fireman BH, Ciuryla V, Black SB. Cost-effectiveness of pneumococcal conjugate vaccine: evidence from the first 5 years of use in the United States incorporating herd effects. *The Pediatric infectious disease journal* 2006; 25:494-501.
28. Vestrheim DF, Lovoll O, Aaberge IS, Caugant DA, Hoiby EA, Bakke H, Bergsaker MR. Effectiveness of a 2+1 dose schedule pneumococcal conjugate vaccination programme on invasive pneumococcal disease among children in Norway. *Vaccine* 2008; 26:3277-81.
29. Ray GT, Pelton SI, Klugman KP, Strutton DR, Moore MR. Cost-effectiveness of pneumococcal conjugate vaccine: an update after 7 years of use in the United States. *Vaccine* 2009; 27:6483-94.
30. McIntosh ED, Conway P, Willingham J, Hollingsworth R, Lloyd A. Pneumococcal pneumonia in the UK--how herd immunity affects the cost-effectiveness of 7-valent pneumococcal conjugate vaccine (PCV). *Vaccine* 2005; 23:1739-45.
31. De Wals P, Black S, Borrow R, Pearce D. Modeling the impact of a new vaccine on pneumococcal and nontypable *Haemophilus influenzae* diseases: a new simulation model. *Clinical therapeutics* 2009; 31:2152-69.
32. Rozenbaum MH, Hoek AJ, Hak E, Postma MJ. Huge impact of assumptions on indirect effects on the cost-effectiveness of routine infant vaccination with 7-valent conjugate vaccine (Prevnar((R))). *Vaccine* 2010; 28:2367-9.
33. Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in

England and Wales: an observational cohort study. *The Lancet infectious diseases*; 11:760-8.

34. Strutton DR, Farkouh RA, Earnshaw SR, Hwang S, Theidel U, Kontodimas S, Klok R, Papanicolaou S. Cost-effectiveness of 13-valent pneumococcal conjugate vaccine: Germany, Greece, and The Netherlands. *The Journal of infection* 2012; 64:54-67.

35. Tarmed Switzerland. Olten, 2004.

36. The hospitals of Switzerland - Tariffs and Prices. Berne, Switzerland.

37. Documed. Compendium Switzerland. CH-Basel.

38. Tarmed Switzerland 01.07.00, 01.04.2010. Olten, 2004.

39. FSO. Federal Statistical Office (Bundesamt für Statistik): Statistisches Jahrbuch der Schweiz 2001. Zurich: Verlag Neue Zuercher Zeitung, 2001.

40. BFS. Swiss Federal Statistic Office - Medical statistics of hospitals Erwin Wueest, 2005.

41. Bennett JE, Sumner W, 2nd, Downs SM, Jaffe DM. Parents' utilities for outcomes of occult bacteremia. *Archives of pediatrics & adolescent medicine* 2000; 154:43-8.

42. Bovier PA, Wyss K, Au HJ. A cost-effectiveness analysis of vaccination strategies against *N. meningitidis* meningitis in sub-Saharan African countries. *Social science & medicine* (1982) 1999; 48:1205-20.

43. Harris A, Hendrie D, Bower C, Payne J, de Klerk N, Stanley F. The burden of *Haemophilus influenzae* type b disease in Australia and an economic appraisal of the vaccine PRP-OMP. *The Medical journal of Australia* 1994; 160:483-8.

44. Oh PI, Maerov P, Pritchard D, Knowles SR, Einarson TR, Shear NH. A cost-utility analysis of second-line antibiotics in the treatment of acute otitis media in children. *Clinical therapeutics* 1996; 18:160-82.

45. Vold Pepper P, Owens DK. Cost-effectiveness of the pneumococcal vaccine in the United States Navy and Marine Corps. *Clin Infect Dis* 2000; 30:157-64.

46. Maddigan SL, Feeny DH, Johnson JA. Health-related quality of life deficits associated with diabetes and comorbidities in a Canadian National Population Health Survey. *Qual Life Res* 2005; 14:1311-20.

47. Rozenbaum MH, Sanders EA, van Hoek AJ, Jansen AG, van der Ende A, van den Dobbelen G, Rodenburg GD, Hak E, Postma MJ. Cost effectiveness of pneumococcal vaccination among Dutch infants: economic analysis of the seven valent pneumococcal conjugated vaccine and forecast for the 10 valent and 13 valent vaccines. *BMJ (Clinical research ed)* 2010; 340:c2509.

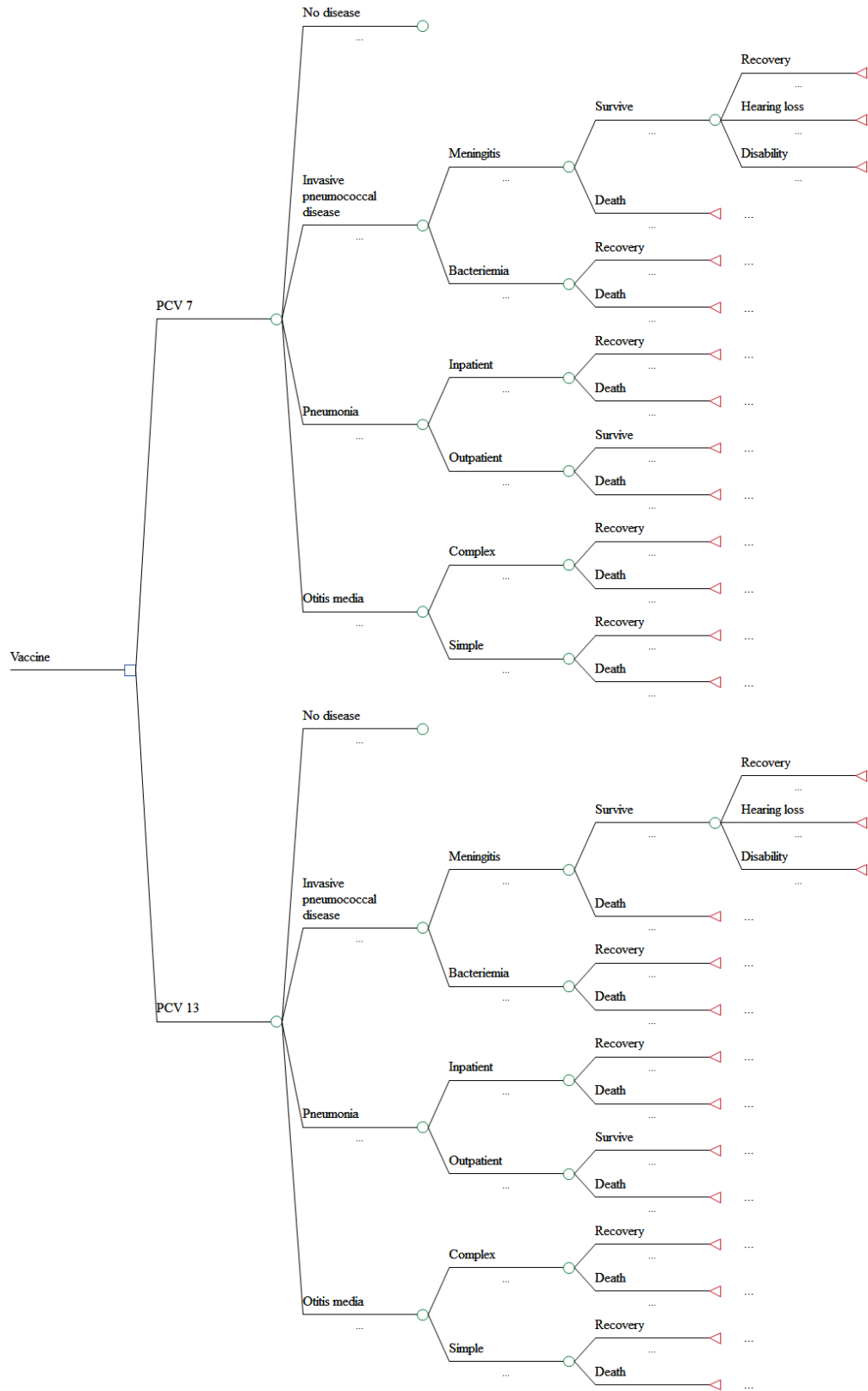
48. Roussy JP KH, Earnshaw SR, Farkouh RA, Hwang S, Strutton D. Cost-effectiveness of 13-valent pneumococcal conjugate vaccine compared with 10-valent vaccine in preventing pneumococcal infections in Quebec. ICAAC. Boston, USA, 2010.

49. Rubin JL, McGarry LJ, Strutton DR, Klugman KP, Pelton SI, Gilmore KE, Weinstein MC. Public health and economic impact of the 13-valent pneumococcal conjugate vaccine (PCV13) in the United States. *Vaccine* 2010.

50. Silfverdal SA, Berg S, Hemlin C, Jokinen I. The cost-burden of paediatric pneumococcal disease in Sweden and the potential cost-effectiveness of prevention using 7-valent pneumococcal vaccine. *Vaccine* 2009; 27:1601-8.

51. Hubben GA, Bos JM, Glynn DM, van der Ende A, van Alphen L, Postma MJ. Enhanced decision support for policy makers using a web interface to health-economic models--illustrated with a cost-effectiveness analysis of nation-wide infant vaccination with the 7-valent pneumococcal conjugate vaccine in the Netherlands. *Vaccine* 2007; 25:3669-78.
52. Claes C, Reinert RR, von der Schulenburg JM. Cost effectiveness analysis of heptavalent pneumococcal conjugate vaccine in Germany considering herd immunity effects. *Eur J Health Econ* 2009; 10:25-38.

Figure 1.



Figures 2 a/b.

