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1 **TITLE PAGE**

2 **TITLE:** Choosing between 7-, 10- and 13-valent Pneumococcal Conjugate Vaccines in
3 Childhood: a review of economic evaluations (2006-2014)

4

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29

30

31

Abstract

Background

33 Seven-valent pneumococcal conjugate vaccines (PCV7) have been used in children for more
34 than a decade. Given the observed increase in disease caused by pneumococcal serotypes
35 not covered by PCV7, an increasing number of countries are switching from 7-valent to 10
36 and 13-valent PCVs ("PCV10" and "PCV13"). Economic evaluations are important tools to
37 inform decisions and price negotiations to make such a switch.

38

Objective

40 This review aims to provide a critical assessment of economic evaluations involving PCV10 or
41 PCV13, published since 2006.

42

Methods

44 We searched Scopus, ISI Web of Science (SCI and SSCI) and Pubmed to retrieve, select and
45 review relevant studies, which were archived between 1st January 2006 and 31st January
46 2014. The review protocol involved standard extraction of assumptions, methods, results
47 and sponsorships from the original studies.

48

Results

50 Sixty-three economic evaluations on PCVs published since January 2006 were identified.
51 About half of these evaluated PCV10 and/or PCV13, the subject of this review. At current
52 prices, both PCV13 and PCV10 were likely judged preferable to PCV7. However, the
53 combined uncertainty related to price differences, burden of disease, vaccine effectiveness,
54 herd and serotype replacement effects determine the preference base for either PCV10 or
55 PCV13. The pivotal assumptions and results of these analyses also depended on which
56 manufacturer sponsored the study.

57

58 **Conclusion**

59 A more thorough exploration of uncertainty should be made in future analyses on this
60 subject, as we lack understanding to adequately model herd and serotype replacement
61 effects to reliably predict the population impact of PCVs. The introduction of further
62 improved PCV's in an environment of evolving antibiotic resistance and under the continuing
63 influence of previous PCVs implies that the complexity and data requirements for relevant
64 analyses will further increase. Decision makers using these analyses should not just rely on
65 an analysis from a single manufacturer.

66

67 **Word count (296)**

68

69 **Keywords:** pneumococcal conjugate vaccine, streptococcus pneumonia, cost-effectiveness,
70 cost-benefit

71

72 **Abbreviations:** PCV – pneumococcal conjugate vaccines, PCV7 -7-valent pneumococcal
73 conjugate vaccine, PCV10 – 10-valent pneumococcal conjugate vaccine, PCV13 – 13-valent
74 pneumococcal conjugate vaccine

75 1.0 Introduction

76 *Streptococcus pneumoniae* is a bacterial pathogen, with over 90 known serotypes. It causes
77 invasive pneumococcal disease (IPD) such as meningitis, bacteraemia, sepsis and peritonitis
78 as well as generally milder non-invasive diseases such as pneumonia and acute otitis media
79 (AOM) [1, 2]. Treatment of pneumococcal disease is increasingly difficult due to rising
80 antibiotic resistance [3, 4].

81

82 A first pneumococcal conjugate vaccine (PCV) was introduced in the US in 2000 and this 7-
83 valent PCV (PCV7) contains capsular polysaccharide antigens of seven serotypes (4, 6B, 9V,
84 14, 18C, 19F and 23F). At the time of the introduction, these 7 types were responsible for
85 80-90% of IPD among children less than 5 years in the US and Western Europe [5]. The
86 introduction of PCV7 vaccination in the US infant vaccination schedule not only substantially
87 reduced IPD cases in vaccine recipients but also in the unvaccinated population through
88 herd effects due to the reduced circulation of *S. pneumoniae* in all age groups following
89 widespread vaccination of children. However, the use of PCV7 also led to an increase of IPD
90 due to serotypes that were not included in the vaccine ("non-vaccine serotypes"), which
91 thus gave rise to a "replacement effect" observed among both the vaccinated and the
92 unvaccinated [6]. This led to the emergence of non-PCV7 vaccine serotypes. The extent of
93 both herd and serotype replacement effects is country-specific [7].

94

95 Since 2010, two improved pneumococcal conjugate vaccines (PCVs) received market
96 authorization in many countries, including in the US and the EU. These vaccines cover the 7
97 serotypes included in the PCV7 vaccine, and additional serotypes responsible for an
98 increasing proportion of IPD. Specifically, PCV10 ("Synflorix™", GSK) contains additional
99 antigens from serotypes 1, 5 and 7F. The manufacturer claims a high protective effect
100 against diseases not only due to pneumococcal serotypes but also against disease (most

101 notably AOM) due to non-typeable *Haemophilus influenzae* (NTHi). PCV13 ("Prevenar13™",
102 Pfizer) contains antigens from serotypes 1, 3, 5, 6A, 7F and 19A in addition to the PCV7
103 serotypes.

104

105 The clinical advantage of each vaccine is difficult to establish for each setting in which their
106 use is considered. PCV10 may provide a higher protection against AOM, while PCV13 offers a
107 wider coverage of serotypes causing IPD [8, 9]. In relation to the latter, serotype 19A is of
108 particular interest in many countries. The manufacturer of PCV10 claims that through
109 coverage of related serotype 19F (also included in PCV7 and PCV13), PCV10 induces cross-
110 protection against 19A IPD. This claim seems to be confirmed by recent studies in Brazil,
111 Finland and Quebec [10-12], Recent data from the US and Europe show that herd immunity
112 against 19A IPD has been induced by PCV13 use [13], but this has not been shown through
113 PCV10 use. The choice between these vaccines must be made in a context of uncertainty
114 regarding future serotype replacement, and differential vaccine prices. Policy should be
115 based on population effectiveness, budget-impact, equity and cost-effectiveness. This paper
116 aims to review all published economic evaluations of pediatric PCV10 and/or PCV13 from
117 2006 to 2014, and therefore focuses primarily on the aspect of cost-effectiveness.

118

119 **2.0 Methods**

120 An initial review of economic evaluations on PCVs predating 2006 [14], was followed by
121 more recent reviews. However, these reviews had a particular focus, such as AOM [15], herd
122 effects [16], studies from one country [17], a small group of countries [18], European
123 countries [19] or modeling assumptions [20].

124

125 All cost data were converted to 2013 US dollars, based on Consumer Price Indices and
126 exchange rates [21, 22].

127

128 *2.1 Search strategy*

129 A literature search was undertaken using the broad combined search string “pneumococc*
130 AND conjugat* AND (vaccin* OR immun*) AND “economic OR cost-effectiveness OR cost-
131 benefit OR cost-utility OR cost-effectiveness OR cost-benefit OR cost-utility” in abstract, title
132 or keyword fields of three databases: Scopus, ISI Web of Science (SCI and SSCI) and Medline
133 (Pubmed) to retrieve studies of potential interest from 1st January 2006 up to 31st January
134 2014 (Figure 1).

135

136 *2.2 Selection*

137 All initially identified studies were considered based on title and abstract, and included for
138 further review if they contained a full economic evaluation [23] and evaluated a PCV covering
139 more than 7 serotypes for use in children (<12 years). Non-English articles were excluded. A
140 flow chart showing the selection process is illustrated in Figure 1.

141

142 *2.3 Data Extraction*

143 The inclusion criteria were checked by two reviewers (DBCW, PB), and data were extracted
144 by either DBCW or PB using a standardized template. In case of doubt, there was a
145 consultation process to base the extraction upon consensus.

146

147 **3.0 Results**

148 *3.1 General study characteristics*

149

150 We identified 63 economic evaluations published since January 2006 [24-86]. Thirty-one
151 studies (49%) evaluated only PCV7, and were therefore excluded [56-86]. Four non-English
152 studies on PCV10 and PCV13 were also excluded [52-55].

153

154 General study characteristics for the remaining 28 publications are presented in Table 1.

155 These studies were made for countries covering 5 continents (7 in North America [24-27, 35,
156 36, 41]; 6 in South America [27, 29, 33, 38, 41, 50]; 6 in the Asia-Pacific [31, 32, 41, 43, 47, 48,
157 51]; 3 in Africa [28, 41, 49]; and 12 in Europe [27, 30, 34, 35, 37, 39-42, 44-46]).

158

159 *3.2 Main assumptions and results*

160 Eighteen studies provided analysis of both PCV13 and PCV10 [25, 28, 30-32, 35-41, 45, 46,
161 48-51]. Seven studies included only PCV13 [26, 33, 34, 42-44, 47] while two studies only
162 focused on PCV10 [27, 29]. One study compared PCV11 with PCV7.

163 It is important to use the correct comparator in economic evaluations. For the PCV choices
164 faced, a direct comparison of all potential PCV candidates is therefore essential [14]. Limiting
165 the analysis to one PCV candidate, or using “no vaccination” as a comparator, when the
166 current situation or the next best alternative is different is fundamentally misleading. At the
167 time these studies were made, in most countries it would be most relevant to health policy
168 to make an incremental CEA of using PCV13 versus PCV10 versus PCV7 [87-99]. As table 2
169 shows, many analyses did not use a relevant incremental approach, reporting the cost-
170 effectiveness of one or two vaccines versus “no vaccination”, and not all feasible options
171 incrementally versus the next best alternative at the time of the study.

172

173 Of the 28 economic evaluations [24-51], 10 studies were cost-utility analyses (CUA) [24-26,
174 31, 32, 36, 37, 44, 45, 48], 7 were CEA [28, 29, 33, 38, 41, 43, 49], and 11 studies provided
175 both CEA and CUA findings [27, 30, 34, 35, 39, 40, 42, 46, 47, 50, 51]. Twelve studies were
176 conducted from a healthcare system or payer’s [25, 31, 32, 34, 36, 39, 42, 44-46, 50, 51] and
177 11 from a societal [24, 26-28, 30, 37, 38, 41, 47-49] perspective, while 5 studies adopted
178 both perspectives [29, 33, 35, 40, 43]. The adoption of multiple perspectives enables the

179 comparison of economic impact with and without incorporating indirect cost due to loss of
180 productivity.

181

182 In terms of time horizon, 5 studies projected outcomes over 1 year [25, 27, 39, 45, 46], 4
183 studies for 5 years [28, 32, 40, 47], 4 studies for 10 years [26, 42, 43, 51], 4 studies for 20
184 [33], 25 [29], 30 [44] and 100 years [31], respectively. Ten studies used lifetime as a time
185 span [24, 30, 34-38, 41, 48, 50]. Most studies applied discount rates between 3% to 6% to
186 cost and benefits. In all 5 studies with 1-year projection, costs and outcomes were not
187 discounted.

188

189 Based on a case-control study in the US [100] and immunogenicity data showing general
190 non-inferiority of 2+1 dose regimen to 3+1 regimen [101, 102], the former schedule has
191 become an acceptable practice, and was evaluated in the base-case analysis in many studies.
192 PCV10 was initially only licensed under a 3+1 schedule in a number of countries. Thus either
193 the 3+1, 3+0, or 2+1 PCV10 or PCV13 schedule was evaluated in comparison to “no
194 vaccination” or the existing PCV7 regimen.

195

196 Different durations of protection by the vaccine were assumed, usually in accordance with
197 the time horizon (except implicitly at 1 year in the five 1-year studies) ranging from 2 to 10
198 years.

199

200 Explicit cost-effectiveness thresholds are not available in many countries, Many studies
201 have used the maximum willingness to pay of 3 times Gross Domestic Product per capita,
202 recommended by the World Health Organization CHOICE (CHOosing Interventions that are
203 Cost-Effective) group [26, 32, 33, 38, 41, 43, 47, 48, 50, 51] while some other studies
204 adopted country-specific thresholds [30, 44, 49]. Yet other studies focused on establishing

205 technical rather than allocative efficiency by just comparing PCV13 and PCV10 to PCV7 [39]
206 or to no vaccination [27, 30]. Under this approach, the vaccine with the smallest incremental
207 cost-effectiveness ratio (ICER) was considered the more cost-effective of the two, without
208 making a judgment about their cost-effectiveness versus other health care programmes. The
209 remaining studies showed cost-savings, thus requiring no threshold.

210

211 In head to head comparative analyses, the assumed differences in vaccination costs
212 (consisting of differences in vaccine price and not in administration costs, given equal
213 vaccination schedules) between PCV10 and PCV13 were highly influential. Tables 2 and 3
214 show the wide range of vaccine prices and the lack of threshold or scenario analyses on
215 vaccination costs.

216

217 In Table 3, it can be seen that almost all studies conducted one-way sensitivity analysis. Only
218 7 studies conducted threshold analysis [24, 27, 29, 30, 36, 40, 44, 47]. Fourteen studies
219 provided probabilistic sensitivity analysis [25, 28, 30, 31, 35, 38, 40, 43-45, 47, 49-51] , 8 of
220 which also provided cost-effectiveness acceptability curves [28, 30, 31, 38, 40, 43, 44, 47].
221 Seventeen studies performed scenario analysis [28-34, 36-40, 44, 46, 47, 50, 51]. Most of the
222 latter studies adjusted vaccine effectiveness based on herd effects (14 studies), and serotype
223 replacement (5 studies). Further adjustments were made regarding cross protection from 6A
224 and/or 19A (5 studies), effects on NTHi (3 studies) and serotype 3 (2 studies). Several studies
225 have considered changes in vaccination costs (6 studies), inclusion of indirect costs (3
226 studies), and varying discount rates (3 studies).

227

228 Vaccination coverage is unlikely to affect the cost-effectiveness ratio in static models [103].
229 In most analyses, vaccination coverage was assumed based on the immunization coverage of
230 the ongoing programme (varying from 80% to 100%).

231

232 *3.3 Burden of Disease*

233 The description of burden of disease is detailed in Appendix A. Most studies presented
234 burden of disease estimates for IPD, all-cause pneumonia and AOM across all age groups.
235 Five studies reported estimates of the incidence and case-fatality ratios (CFRs) for all IPD in
236 general (including pneumococcal meningitis, bacteraemia, sepsis, peritonitis) [29, 31, 42-44]
237 while other studies limited the burden of disease to pneumococcal meningitis and/or
238 bacteraemia. One study investigated the disease burden of AOM only [24]. The incidence
239 trends of IPD, pneumococcal meningitis and bacteremia were similar across studies, showing
240 the typical U-shaped age distribution. All but one study [36] used country-specific CFRs of
241 IPD and all-cause hospitalized pneumonia. All studies assumed outpatient all-cause
242 pneumonia to be non-fatal.

243

244 Most studies included long-term sequelae due to IPD, such as hearing loss and neurological
245 seizures. Seven studies [32, 33, 35, 39, 41, 49, 50] extrapolated long-term meningitis-related
246 sequelae from Australian data [104], a meta-analysis [105-107], the Gambia [108], Delphi
247 panels from Chile, Brazil, Mexico and Columbia [109] and the UK [110] due to scarcity of
248 local data. One Turkish study [45] compared results without and with the inclusion of
249 meningitis-related sequelae using estimates from a meta-analysis [111] and US data [45,
250 112].

251

252 Since pneumococcal pneumonia is often unreliably diagnosed and coded, many studies used
253 all-cause hospitalized pneumonia and all-cause outpatient pneumonia. Most studies also
254 used all-cause AOM whereas the use of tube placement as an outcome was less common.

255

256 *3.4 Vaccine effectiveness*

257 At the time of the studies under review, there were no published randomized controlled trial
258 data, which assessed the clinical efficacy of either PCV13 or PCV10 against IPD. However,
259 GSK's COMPAS and the FinIP trials have recently reported such data for PCV10 [113-116]. In
260 economic evaluations up to January 2014, the effectiveness against IPD was calculated for
261 both PCV10 and PCV13 based on the pivotal efficacy studies of PCV7 [117-119], using a
262 linear adjustment for serotype coverage in the country where the economic evaluation was
263 carried out. Furthermore in studies sponsored by the manufacturer of PCV10 (GSK), PCV10
264 was assumed to offer cross-protection against 19A. This assumption was not made in studies
265 sponsored by Pfizer. There are also two major assumptions regarding vaccine efficacy against
266 non-IPD. In the absence of clinical data on the efficacy of PCV13 against pneumonia and
267 AOM, it is a general assumption that the efficacy of both vaccines would increase
268 proportionally with the increase in serotype coverage for IPD [28, 30-33, 35, 37-39, 42, 43,
269 45-48, 50]. However, the serotypes that typically cause IPD do not necessarily cause AOM
270 and pneumonia to the same extent. On the other hand, studies sponsored by GSK assumed
271 considerable additional effectiveness of PCV10 versus AOM associated with NTHi. The ability
272 of PCV10 or PCV13 to prevent additional clinical non-invasive diseases is important to public
273 health, as due to the very high incidence of these diseases compared to IPD, it could have a
274 large impact on the avoided treatment costs and quality-adjusted life years (QALYs) gained.

275

276 Furthermore, none of the reviewed studies adjusted direct vaccine effectiveness by
277 serotype-specific immunogenicity. Instead, they assumed that the additional effectiveness
278 on IPD caused by the additional serotypes would be the same (sometimes the average) for
279 the 7 serotypes in PCV7 (as shown in Table 2, most assumed this to be 94% or 97.4% for the
280 additional serotypes). Studies attempting to estimate effects on AOM and pneumonia
281 assumed that the serotype distribution in patients with AOM and pneumonia is the same as
282 the distribution of serotypes observed for IPD. Since the effectiveness of PCV10 against

283 AOM remained largely unexplored, head-to-head analyses tended to conclude that PCV13
284 was more cost-effective than PCV10 without including the benefits of NTHi-related diseases,
285 though Chuck et al [25] noted this is reversed, if they assumed an effect on NTHi AOM.

286

287 Although childhood PCV7 vaccination induced herd effects in the rest of the population [120],
288 7 studies did not include such indirect protection [24, 28, 29, 33, 38, 42, 45]. Therefore in
289 these studies the impact of the existing PCV7 programme and the projected PCV10 or PCV13
290 impact on the burden of disease are restricted to vaccinated individuals below 5 years of age.
291 In most studies, it was assumed that herd effects of PCV10 and PCV13 for IPD observed in
292 the respective countries were similar to those of PCV7 observed in the US. One study in
293 Australia [31], however, applied the observed country-specific herd effect using their
294 national database. The extrapolated or observed herd effect estimates were then adjusted
295 using the country-specific serotype coverage. Five studies [25, 30, 35, 40, 46] assumed herd
296 effects for IPD only. Only two studies [43, 44] used a transmission dynamic model to
297 explicitly account for herd effects. Due to the uncertainty of assumptions to derive country-
298 specific herd effect estimates, some studies have tested their assumptions in scenario
299 analysis [26, 31-34, 36, 38, 42, 43, 48].

300

301 *3.5 Model structure*

302 Only 2 out of 28 studies [43, 44] used a transmission dynamic model, capable of, mimicking
303 herd effects from vaccination. This is not possible with static models [14, 103] [121]. Some
304 authors applied an external herd immunity factor (sometimes combined with serotype
305 replacement) in a static population model, and combined this with estimating the direct
306 effects in a single ageing cohort. In those static population models, the anticipated indirect
307 effects, i.e. herd effects combined with serotype replacement was incorporated by assuming
308 it to be similar to empirical observations elsewhere (usually, in the US [120]). It is disputable

309 that these observed indirect effects can be transferred between geographic settings.
310 Moreover, some studies assumed the different PCV formulations induced exactly the same
311 indirect effect, and therefore argued that such effect canceled out in comparisons between
312 PCVs [27, 35, 37, 49, 50]. The implicit assumption here is then that the addition of a different
313 number of serotypes does not differentially influence indirect effect in the population. This
314 assumption is flawed, because there is likely to be a different indirect effect from using
315 PCV13 versus PCV10 and PCV7, especially in view of serotype replacement in places where
316 PCV7 has been used for several years. Two PCV 10 studies [25, 27] used a “steady-state
317 static population model” [122], assuming that the direct and indirect effects of different
318 vaccination options can be estimated over a one year time period from a steady state year in
319 the future, for the total population. However, the changing epidemiology of diseases over
320 time cannot be addressed due to the cross-sectional nature of this modeling design.

321

322 It is beyond our scope to discuss mathematical models without economic evaluation in
323 detail, but most of those we identified [123-137] presented conceptual explorations for
324 dynamic models [123] or compared static models [124, 125, 130, 131], or demonstrated
325 specific transmission dynamic features of pneumococci [126, 128, 129, 134, 136], as did
326 previous pre-2006 models [135, 137]. Only three were applications to PCVs.

327 Melegaro et al and Snedecor et al both developed an age structured compartmental
328 deterministic model [127, 132]. Snedecor et al did not distinguish vaccine serotypes from
329 non-vaccine serotypes, and focused on reproducing the observed herd effect impact in the
330 US, by distinguishing IPD and nasopharyngeal carriage as pneumococcal infection states.
331 Snedecor et al’s approach did not account for serotype replacement. In order to fit the
332 observed data on herd effects (US, 2000-2005), they departed from the mass action
333 principle used widely in transmission dynamic modelling and defined the force of infection
334 in the oldest age group to be proportional to the squared number of carriers in the youngest

age group. Melegaro et al distinguished PCV7 vaccine serotypes from non-vaccine serotypes, and their model was used in the economic evaluation by Van Hoek et al [44]. Nurhonen et al [133] has applied a network model of *S. pneumoniae*, of which the demographic component originated from a *Haemophilus influenzae* type b –model [138] to derive the net effectiveness of PCV7, PCV10 and PCV13 vaccination, accounting for the interplay of serotype replacement and herd immunity.

341

3.6 Sponsorship

In view of the different claims on effectiveness by the respective manufacturers, sponsorship has a large impact on the assumptions being made and the main results being communicated. Of nine Pfizer-sponsored articles, four [25, 36, 39, 46] show that PCV13 dominates PCV10 (i.e. PCV 13 saves costs and gains health compared to PCV10), three [26, 34, 42] show that PCV13 dominates or is cost-effective versus PCV7 (or exceptionally no vaccination), and two others show that PCV13 and PCV10 are both cost-effective compared to no vaccination [33], and compared to PCV7 [40]. Of eight GSK-sponsored articles, six show that PCV10 dominates PCV13 [30, 35, 37, 45, 50, 51]. One study shows that PCV10 is more cost-effective versus PCV13 [31] and one other that PCV10 dominates PCV7 [27]. Of eleven “independent” publications [24, 28, 29, 32, 38, 41, 43, 44, 47-49], four have no dominant message [28, 38, 41, 49] but show the impact of pivotal assumptions on the results (indicating that the inclusion of these assumptions change the preference for one or the other vaccine if health gains are expressed as QALYs). One study showed that PCV13 is most cost-effective when compared to PCV10 and PCV7 [32], and two others that PCV13 has acceptable cost-effectiveness compared to PCV7 [44, 47]. The oldest of these publications made a hypothetical analysis of PCV11, and concluded that it dominates PCV7 [24]. Lastly, one study showed that both vaccines were not cost-effective even with the inclusion of herd effects [48].

361

362 **4.0 Discussion**

363 We reviewed published economic evaluations of pediatric PCV10 and PCV13 from 2006 to
364 2014, appraising basic assumptions, model structures, burden of disease and influence of
365 sponsorship. Most evaluations were limited due to data or methodological constraints, some
366 of which can be considered important flaws. First, 8 studies [25, 29, 36, 38, 39, 42, 43, 46]
367 did not consider serotype replacement, which could substantially offset herd effects. The
368 degree of serotype replacement was one of the most influential factors in studies accounting
369 for it. Second, most studies did not perform sensitivity analyses on vaccination costs, which
370 are highly influential. Third, many studies did not explore the impact of different
371 assumptions for the comparative effectiveness of the vaccines, which is important since
372 clinical impact data on PCV10 and PCV13 were scarce when these studies were performed.

373

374 Of the 28 studies, 17 were funded by industry (Table 1). We observed that all “Pfizer studies”
375 published positive messages on PCV13, and that all “GSK studies” reported positive
376 messages on PCV10. Independent studies tended to provide a more balanced view,
377 investigating the impact of assumptions that led to the manufacturers’ opposing conclusions.
378 Essentially, PCV10 can be shown to be more cost-effective than PCV13 by assuming an
379 important effect of PCV10 on NTHi-related IPD and NTHi-related AOM. The main uncertainty
380 then stems from the definition of AOM as it is captured through a country’s surveillance
381 system, and how this relates to the clinical trials’ estimate of efficacy against it. But PCV13
382 can also be shown to be more cost-effective than PCV10 in countries where the serotype
383 coverage for the three additional PCV13 serotypes is substantial (especially serotype 19A), or
384 if the herd effects are assumed to apply mainly to IPD, and is relatively little influenced by
385 serotype replacement, or if PCV10’s potential impact on NTHi AOM is ignored or downplayed
386 (e.g., by focusing on mortality, or life years gained as an endpoint instead of QALYs). The

387 previously noted difficulties of conducting unbiased cost-effectiveness research for PCV7
388 thus seem to persist for PCV10 and PCV13 [139].

389

390 The etiopathogeny of pneumococcal diseases is particularly complex and serotype specific,
391 and currently the understanding to adequately model the serotype-specific effects of
392 carriage, disease, herd immunity and replacement is insufficient to reliably predict the
393 population impact of PCVs. A virtually universal limitation was the use of a static model, in
394 which indirect effects need to be assumed externally, rather than being generated by the
395 model. Most static model studies have used indirect effect estimates from the US. Although
396 after 5 years [56] and after seven years [73] the net indirect effects were beneficial in the US
397 (resulting in a very cost-effective PCV7 program), such indirect effects might vary in different
398 time periods and contexts (e.g., social contact patterns, ecological pressures from antibiotic
399 consumption and resistance). Regarding so-called static steady state models [25, 124], it is
400 not clear how the steady state is implicitly defined in these models (i.e. how far in the future
401 the steady state is assumed to be, though implicitly the assumption seems to be that it is
402 reached for PCV7, up to the point where observational data exist). Authors of these studies
403 assert that their approach renders discounting of future costs or effects unnecessary,
404 because they evaluate the cost-effectiveness over a one year period, from the steady state
405 year to the steady state year +1. That is, the future outcomes earned by a series of
406 previously vaccinated cohorts are balanced against the costs of vaccinating a cohort in the
407 present. Yet, investment is made in the first vaccinated cohort for a number of years before
408 reaching the steady state year. Hence, it is difficult to disentangle time preference effects
409 under this approach. Even if time preference up to the steady state year would not need to
410 be accounted for, by assuming that the steady state year represents an average year in the
411 present, these analyses estimate the number of life years and QALYs foregone due to
412 mortality in the one year time period between the steady state year and the steady state

413 year+1. Transmission dynamic models have been rarely used for pneumococcal infections,
414 because they require data on age-specific carriage of pneumococcal serotypes in healthy
415 and diseased people alike. If such data are not available, serotype specific issues are ignored.
416 For instance, Wu et al [86] projected outcomes in the absence of serotype-specific
417 information. This is of academic interest, but is problematic if one wants to validate the
418 model and assess the impact of vaccines with different serotype coverage. Van Hoek et al
419 [44] applied a serotype-specific dynamic transmission model for England and Wales, using
420 carriage data from a 10-month longitudinal household study of pre-school children and their
421 families in Hertfordshire, England from 2001 to 2002. As herd effects depend on the
422 assumed social contact structure [140], one of the major strengths of using transmission
423 dynamic models is the ability to produce country-specific herd effects without having to
424 extrapolate this entirely from foreign sources.

425

426 It is worth noting that a difficulty in economic comparisons between PCV10 and PCV13 is the
427 lack of head-to-head clinical comparisons between these vaccines. To our knowledge, there
428 has been no comparative trial and till now they have been used sequentially only in Quebec
429 and Ontario [141, 142] where the real-world PCV effectiveness was evaluated using
430 population-based surveillance for IPD. Observations from such locations could prove useful
431 to better inform future PCV modelling studies.

432

433 Many economic analyses did not explore the potential differential effectiveness of 3+1
434 versus 2+1 schedules, but assumed that both are equally effective. However, a two dose
435 primary schedule is somewhat less immunogenic than a 3 dose primary schedule, and a US
436 cohort study also reported pre-boosting more hospital admissions for lower respiratory
437 tract infections with 2 versus 3 dose priming [143]. This difference disappears if vaccine
438 uptake is high with subsequent herd effects.

439

440 A limitation of our review is that we only included studies that are published in peer-
441 reviewed journals. Yet, increasingly government agencies commission policy-supporting
442 reports that are peer-reviewed, but are not necessarily translated into journal publications.
443 Some of these reports are very extensive and explore uncertainty into far more detail (eg see
444 [144]).

445

446 We conclude that both PCV13 and PCV10 were likely to be judged preferable to the current
447 situation (i.e. often PCV7). Which of these two to choose is less clear, due to fundamental
448 uncertainties on serotype replacement and herd effects, serotype cross-protection and NTHi
449 AOM protection. Essentially it depends on the price difference between both vaccines, and
450 the weight policy makers wish to attach to potentially preventing extra IPD cases through
451 PCV13 use versus extra AOM cases through PCV10 use.

452

453 **Conflict of interest**

454 DBCW received funding from Pfizer and GSK during 2012-2013 to conduct cost-effectiveness
455 analysis of PCV13 and PCV10. A university chair in PB's centre at the University of Antwerp
456 (UA) was supported in 2009-2014 by a gift from Pfizer. There is no connection between the
457 research of the chair holder (Niel Hens) and this paper. UA also received an unrestricted
458 research grant (2012) from Pfizer to analyse hospitalization costs for pneumonia in Belgium.
459 All other authors have no conflict of interest to declare.

460

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465

466 **List of figures**

467 **Figure 1** Flow diagram of the selection process to identify studies to be included (1st January

468 2006 – 31st January 2014)

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892

Appendix A. Burden of disease of published economic evaluations of pneumococcal conjugate vaccine (1st January 2006- 31st January 2014)

First author, country, year	Incidence of IPD (per 100,000 population)		Case-fatality ratios (%)			Inclusion of sequelae			
	All IPD	Meningitis	Bacteremia	IPD	Non IPD				
O'Brien, US, 2009	N/R	N/R	N/R	Only report AOM results	Meningitis	Bacteremia	Other	Pneumonia	
Chuck, Alberta, 2010	<2 y:	N/A	N/A	N/A	<2 y: 6.5	<2 y: 2	N/A	<2 y: 1	No
	3.67/1.09/2.23/8.98								
	2-4 y:				2-4 y: 6.5	2-4 y: 2		2-4 y: 1	
	2.31/1.66/2.89/2.86								
	5-9 y:				5-9 y: 6.5	5-9 y: 1.6		5-9 y: 1	
	0.59/0.27/2.55/1.01								
	10-14 y:				10-14 y: 6.5	10-14 y: 1.6		10-14 y: 1.6	
	0.2/0.34/0.33/0.69								
	15-19 y:				15-19 y: 27.6	15-19 y: 15		15-19 y: 1.6	
	0.09/0.88/0.89/0.37								
20-39 y:				20-39 y: 27.6	20-39 y: 15		20-39 y: 1.6		
0.02/2.78/2.25/2.38									
40-64 y:				40-64 y: 27.6	40-64 y: 15		40-64 y: 1.6		
1.67/3.48/4.11/6.22									
65+ y:				65+ y: 27.6	65+ y: 31		65+ y: 1.6		
5.01/3.34/5.28/15.09									
(PCV7 vs. PCV10 vs. PCV13 vs. Other)									
Rozenbaum, the Netherlands, 2010	<2 y: 34.5	N/R	N/R	N/A	<2 y: 6.5	<2 y: 6.5	N/A	<2 y: 6.5	Meningitis and bacteremia
	2-4 y: 8.1				2-4 y: 6.5	2-4 y: 6.5		2-4 y: 6.5	
	5-49 y: 4.1								
	50-64 y: 16.7								
>65 y: 58.8									
Rubin, US, 2010	3-5 m: 63 (ref17)								
	10-14 y: 1								
	50-54 y: 11								
	60-64 y: 26								
	≥90 y: 97								

1-2 y: 34.72	1-2 y: 6.9	1-2 y: 0.1	1-2 y: 0.1	
2-3 y: 20.13	2-3 y: 4.0	2-3 y: 0.4	2-3 y: 0.2	
3-4 y: 13.09	3-4 y: 14.0	3-4 y: 0.4	3-4 y: 0.2	
4-5 y: 9.34	4-5 y: 4.0	4-5 y: 0.4	4-5 y: 0.2	
5-17 y: 2.42	5-17 y: 10.0	5-17 y: 4.2	5-17 y: 0.3	
18-34 y: 4.34	18-34 y: 10.0	18-34 y: 4.7	18-34 y: 0.7	
35-49 y: 11.46	35-49 y: 11.0	35-49 y: 18.0	35-49 y: 1.7	
50-64 y: 19.82	50-64 y: 11.4	50-64 y: 11.3	50-64 y: 2.5	
65+ y: 37.85	65+ y: 23.8	65+ y: 15.7	65+ y: 6.3	

Talbird, Canada, Germany, Mexico, and Norway, 2010	N/A	<1 y: 19.4/9.7/5.8/19.4 1 y: 4.6/4.6/0.5/6.2 2 y: 10.4/6.0/5.4/4 3 y: 0.7/1.6/0.7/0.8 4 y: 0.5/1.6/0.7/0.8 5-9 y: 0.5/0.5/0.1/0.7 10-14 y: 0.5/0.5/0.1/0.3 15-19 y: 0.4/1.0/0.1/0.3 20-24 y: 0.4/1.0/0.3/0.3 25-29 y: 0.4/1.0/0.3/0.3 30-34 y: 0.4/1.0/0.3/0.7 35-39 y: 0.4/1.0/0.3/0.7 40-44 y: 0.4/1.0/0.3/0.7 45-49 y: 0.4/3.4/0.9/0.7 50-54 y: 0.4/3.4/0.9/2.4 55-59 y: 0.4/3.4/0.9/2.4 60-64 y: 0.4/3.4/0.9/2.4 65-69 y:	<1 y: 94.8/7.6/101.8/49.3 1 y: 78.3/6.8/4/60.7 2 y: 32.6/3.6/8.4/21.0 3 y: 18.5/1.3/9.5/13.6 4 y: 12.8/1.3/9.5/5.8 5-9 y: 4.7/0.4/0.4/4.4 10-14 y: 2.8/0.4/0.4/3.5 15-19 y: 6.6/0.5/1.6/3.5 20-24 y: 6.6/0.5/0.5/3.5 25-29 y: 6.6/0.5/0.5/3.5 30-34 y: 6.6/0.5/0.5/12.6 35-39 y: 6.6/0.5/0.5/12.6 40-44 y: 6.6/0.5/0.5/12.6 45-49 y: 6.6/1.8/2.3/31.6 50-54 y: 6.6/1.8/2.3/31.6 55-59 y: 6.6/1.8/2.3/31.6 60-64 y: 6.6/1.8/2.3/31.6 65-69 y:	N/A	<18 y: 6.5 18+ y: 27.6	<18 y: 1.6 18-65 y: 15 65+ y: 31	N/A	<18 y: 1.6 18-65 y: 15 65+ y: 31	Meningitis
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Kim, the Gambia, 2010	N/A	<2 months: 12.1 2-11 months: 5.2 12-59 months: 0.5	<2 months: 26.62 2-11 months: 10.92 12-59 months: 1.1	N/A	<1 months: 27 1-5 months: 23 6-11 months: 48 12-59 months: 46	All age groups: 35	N/A	All age groups: 3.0	Meningitis
	Sartori, Brazil, 2010	0-1 y: 64.69 1-2 y: 13.81 2-3 y: 9.74 3-4 y: 5.93 4-5 y: 5.84	N/A	N/A	N/A	N/A	N/A	all age groups: 0.8	Meningitis
	Robberstad, Norway, 2011	N/A	<1 y: 19.4 1 y: 6.2	<1 y: 49.3 1 y: 60.7	N/A	<5 y: 9 >5 y: 9.92	<5 y: 0 (with focus): 0.29 (without focus) >5 y: 0.33 (with focus): 9.67 (without focus)	<5 y: 0 >5 y: 0.29	Meningitis
	Newell, Australia, 2011	N/A	2 y: 4.4 3 y: 0.8 4 y: 0.8 5-9 y: 0.7 10-19 y: 0.3 20-29 y: 0.3 30-39 y: 0.7 40-49 y: 0.7 50-59 y: 2.4 60-69 y: 2.4 ≥70 y: 3.2	2 y: 21 3 y: 13.6 4 y: 5.8 5-9 y: 4.4 10-19 y: 3.5 20-29 y: 3.5 30-39 y: 12.6 40-49 y: 12.6 50-59 y: 31.6 60-69 y: 31.6 ≥70 y: 81.5	N/A	N/A	N/A	0 y: 0.002	Meningitis
			1.2/9.6/1.4/2.4 70-74 y: 1.2/9.6/1.4/3.2 75-79 y: 1.2/4.1/1.4/3.2 80-84 y: 1.2/4.1/1.4/3.2 85-89 y: 1.0/10.0/1.4/3.2 ≥90 y: 1.0/10.0/1.4/3.2	34.4/5.1/15.2/31.6 70-74 y: 34.4/5.1/15.2/81.5 75-79 y: 34.4/2/15.2/81.5 80-84 y: 34.4/2.2/15.2/81.5 85-89 y: 53.1/5.3/15.2/81.5 ≥90 y: 53.1/5.3/15.2/81.5					
			0 y: 5.6	0 y: 16.8					
			0-4 y: 0.0201	N/A					
			0 y: 5.6	0 y: 16.8					

Tyo, Singapore, 2011	N/A	0-5 y: 2.2 6-19 y: N/A 20-59 y: N/A 60+ y: N/A	0-5 y: 2.3 6-19 y: 1 20-59 y: 4 60+ y: 25	N/A	0-5 y: 8.6 6-19 y: N/A 20-59 y: N/A 60+ y: N/A	0-5 y: 1 6-19 y: N/A 20-59 y: 20.8 60+ y: 23.1	N/A	0-5 y: 0.6 6-19 y: 1 20-59 y: 7 60+ y: 26 85+ y: 0.1848	Meningitis (Australia data)
Urueña, Argentina, 2011	N/A	<5 y: 3.5	<5 y: 50.6	N/A	<5 y: 14.3	<5 y: 0	N/A	<5 y: 1.1	Meningitis (Meta-analysis)
Diez-Domingo, Spain, 2011	<1 y: 25.7	N/A	N/A	N/A	<1 y: 10 1 y: 6.9 2 y: 6.9 3 y: 4 4 y: 4	<1 y: 0 1 y: 0 2 y: 0 3 y: 0 4 y: 0	N/A	<1 y: 0.5 1 y: 0.5 2 y: 0.5 3 y: 0.5 4 y: 0.5	
	1 y: 30.3								
	2 y: 12.6								
	3 y: 12.6								
	4 y: 2.3								
	5-17 y: 2.3				5-17 y: 10 18-34 y: 12 35-49 y: 15 50-64 y: 17 >65 y: 27	5-17 y: 25 18-34 y: 6.6 35-49 y: 18.2 50-64 y: 30 >65 y: 34.6		5-17 y: 0.5 18-34 y: 7 35-49 y: 7 50-64 y: 12 >65 y: 12	
	18-34 y: 0.8								
	35-49 y: 4.5								
	50-64 y: 4.5								
	>65 y: 8.4								
Nakamura, 77 middle-income countries, 2011	NPM/PPD	<5 y: 14.3/10.2 5-14 y: 17.8/4.98 15-44 y: 2.5/1.3	5-14 y: 60.7/17.0 15-44 y: 8.2/14.29	<5 y: 0.407/0.171	<5 y: 0.519/0.281 5-14 y: 0.0736/0.0712 15-44 y: 0.433/0.419	5-14 y: 0.0205/0.0198 15-44 y: 0.120/0.116	N/A	<5 y: 0.0234/0.0089 5-14 y: 0.0063/0.00641 15-44 y: 0.0389/0.0376	Meningitis (data from high-income countries and Gambia)

Kreier, Canada and the UK, 2012	N/A	<1 yr:19.4 / 9.5	<1 yr:94.8 / 41.8	N/A	<1 yr:6.5 / 5	<1 yr: 1.6 / 4	N/A	<1 yr: 0.1 / 1	Meningitis (UK)
		1 yr:4.6 / 0.6	1 yr:78.3 / 30.9		1 yr: 6.5 / 6.6	1-4 yr: 1.6 / 1		1-4 yr: 0.1 / 0	
		2 yr: 1 / 0.6	2 yr: 32.6 / 10.6		2-4 yr: 6.5 / 5.8	5-19 yr: 1.6 / 0		5-9 yr: 4.7 / 3.5	
		3 yr: 0.7 / 0.6	3 yr: 18.5 / 10.6		5-14 yr: 6.5 / 4.8	20-24 yr: 6.6 / 5.4		10-19 yr: 1.6 / 2	
		4 yr: 0.5 / 0.6	4 yr: 12.8 / 10.3		15-19 yr: 6.5 / 11.5	25-44 yr: 15 / 20		20-44 yr: 15 / 3	
		5-9 yr: 0.5 / 0.3	5-9 yr: 4.7 / 3.5		20-44 yr: 27.6 / 11.5	45-64 yr: 15 / 26		45-64 yr: 15 / 14	
		10-14 yr: 0.5 / 0.1	10-14 yr: 2.8 / 1.6		45-64 yr: 27.6 / 15.9	65-74 yr: 31 / 27		65-74 yr: 31 / 29	
		15-19 yr: 0.4 / 0.2	15-19 yr: 6.6 / 5.3		65+ yr: 27.6 / 30.4	70-74 yr: 34.4 / 23.1		75+ yr: 31 / 46	
		20-44 yr: 0.4 / 0.2	20-24 yr: 6.6 / 5.4			75+ yr: 31 / 40		80-84 yr: 34.4 / 31.8	
		45-59 yr: 0.4 / 0.4	25-29 yr: 6.6 / 5.5					85-89 yr: 53.1 / 67.6	
Earnshaw, Canada, 2012	N/A	60-64:0.4 / 0.5	30-34 yr: 6.6 / 4.8	N/A			N/A		Meningitis
		65-69 yr: 1.2 / 0.7	35-39 yr: 6.6 / 4.4						
		70-74 yr: 1.2 / 0.8	40-44 yr: 6.6 / 4.6						
		75-79 yr: 1.2 / 0.5	45-49 yr: 6.6 / 9.3						
		80-84 yr: 1.2 / 0.1	50-54 yr: 6.6 / 9.9						
		85-89 yr: 1 / 0.3	55-59 yr: 6.6 / 9.3						
		90+: 1 / 0.5	60-64 yr: 6.6 / 12						
			65-69 yr: 34.4 / 20.1						
			70-74 yr: 34.4 / 23.1						
			75-79 yr: 34.4 / 32.6						
Sjöbeck ⁴ Bj, Sweden, 2012	N/A		80-84 yr: 34.4 / 31.8	N/A			N/A		National Board of Health and Welfare, data on file
			85-89 yr: 53.1 / 67.6						
			90+ yr: 53.1 / 115.5						
		0-2 yr: 0.52	0-2 yr: 14.77		0-2 yr: 2	0-2 yr: 1		0-2 yr: 1	
		2-4 yr: 0.37	2-4 yr: 10.62		2-4 yr: 0.3	2-4 yr: 0.3		2-4 yr: 0.3	
		5-17 yr: 0.24	5-17 yr: 6.74		5-17 yr: 0.3	5-17 yr: 0.3		5-17 yr: 0.3	
		18-64 yr: 1.54	18-64 yr: 43.67		18-64 yr: 7	18-64 yr: 7		18-64 yr: 7	
		65+ yr: 3.07	65+ yr: 87.07		65+ yr: 11	65+ yr: 11		65+ yr: 11	

Meningitis and bacteremia

	N/A		N/A	N/A	37	N/A	N/A	7	No
Castañeda-Orjuela, Colombia, 2012	0.00/1		N/A	N/A					Meningitis (Meta analysis)
Stratton, Germany, Greece, and the Netherlands, 2012	0-2 y: 9.75/6.00/16.00	0-2 y: 33.6/16.0/25.71	N/A	0-4 y: 0.08/0.14/0.09	0-4 y: 0.02/0.01/0.09	N/A	0-4 y: 0.00/0.003/0.00		
	2-4 y: 2.21/6.00/1.50	2-4 y: 9.4/16.0/7.5		5-14 y: 0.08/0.05/0.09	5-14 y: 0.02/0.02/0.09		5-14 y: 0.00/0.002/0.01		
	5-9 y: 0.66/0.11/0.60	5-9 y: 3.07/0.30/2.0		15-17 y: 0.08/0.18/0.26	15-17 y: 0.02/0.08/0.08		15-17 y: 0.00/0.008/0.01		
	10-14 y: 0.66/0.11/0.40	10-14 y: 3.07/0.30/1.50		18-29 y: 0.00/0.18/0.26	18-29 y: 0.20/0.08/0.08		18-29 y: 0.01/0.008/0.01		
	15-17 y: 0.66/0.20/0.50	15-17 y: 3.07/0.55/4.90		30-34 y: 0.00/0.15/0.26	30-34 y: 0.20/0.07/0.08		30-34 y: 0.01/0.032/0.01		
	18-29 y: 0.00/0.20/0.50	18-29 y: 6.75/0.55/4.90		35-44 y: 0.00/0.15/0.26	35-44 y: 0.20/0.07/0.08		35-44 y: 0.05/0.032/0.01		
	30-44 y: 0.00/0.36/0.50	30-44 y: 12.15/1.30/4.90		45-49 y: 0.00/0.15/0.21	45-49 y: 0.20/0.07/0.21		45-49 y: 0.05/0.032/0.09		
	45-49 y: 0.00/0.36/1.90	45-49 y: 12.15/1.30/14.60		50-59 y: 0.00/0.09/0.21	50-59 y: 0.20/0.04/0.21		50-59 y: 0.06/0.029/0.09		
	60-64 y: 0.00/1.58/1.90	60-64 y: 22.95/1.69/14.60		≥65 y: 0.00/0.30/0.35	≥65 y: 0.30/0.14/0.39		≥65 y: 0.16/0.69/0.20		

Blank, Switzerland, 2012	<1 yr: 32	N/A	N/A	1-5 yr: 0	1-5 yr: 0	N/A	N/A	1-5 yr: 0	Meningitis
	1-2yr: 8			5-17 yr: 0	5-17 yr: 0			5-17 yr: 0.17	
	2-3 yr: 12			18-34 yr: 0	18-34 yr: 0			18-34 yr: 0.76	
	3-4 yr: 11			35-49 yr: 5.3	35-49 yr: 0			35-49 yr: 2.71	
	4-5 yr: 13			50-64 yr: 8.3	50-64 yr: 28.6			50-64 yr: 11.43	
	5-17 yr: 3			65+ yr: 15	65+ yr: 26.9			65+ yr: 84.93	
	18-34 yr: 3								
	35-49 yr: 8								
	50-64 yr: 14								
	65+ yr: 44								
WU, Taiwan, 2012	0-2 y: 15.2	N/A	N/A	0-2 y: 2	N/A	N/A	N/A	0.38	No
	3-4 y: 17.7			3-4 y: 2.5				0.1	
	5-17 y: 1.4			5-17 y: 0				0.05	
	18-49 y: 0.9			18-49 y: 7.18				0.09	
	50-64 y: 4.2			50-64 y: 15.8				0.27	
Van Hoek, England, 2012	65+ y: 12.1			65+ y: 15.3				0.36	
	0-4 y: 15.1	N/A	N/A	0-4 y: 2	N/A	N/A	N/R	N/R	Meningitis
	5-64 y: 5.8			5-64 y: 27					
	65+ y: 23.9			65+ y: 71					
Bakir, Turkey, 2012	N/A	<1 y: 14.6	<1 y: 339	N/R	N/R	N/R	N/R	N/R	No
		1-2 y: 10	1-2 y: 132						
		2-3 y: 5	2-3 y: 21						
		3-4 y: 5	3-4 y: 21						
		4-5 y: 5	4-5 y: 21						
Kick, Denmark and Sweden, 2013		5-10 y: 1.2	5-10 y: 15.5						
	N/A	Denmark: 0.11-6.16	Denmark: 1.73-56.89	N/R	Denmark: 6-36	Denmark: 1-23	N/R	Denmark: 1-11	Meningitis
		Sweden: 0.06-7.44	Sweden: 1.28-50.02						
Kulpeng, Thailand, 2013	N/A	0-4 y: 0.88	0-4 y: 11.95	Full-text unable to access (ref 23-28)	Sweden: 6-20	Sweden: 6-20		Sweden: 1-6	Meningitis and AOM
		5-9 y: 0.26	5-9 y: 1.38						
		10-14 y: 0.45	10-14 y: 1.38						
		15-19 y: 0.33	15-19 y: 1.38						
		20-24 y: 0.33	20-24 y: 1.87						
		25-34 y: 0.40	25-34 y: 1.87						
		35-44 y: 0.44	35-44 y: 1.87						
		45-49 y: 0.38	45-49 y: 1.87						
		50-54 y: 0.38	50-54 y: 4.77						

5-9 y: 0.2	5-9 y: 1.2	5-9 y: 9.0	5-9 y: 4.6
10-64 y: 0.1	10-64 y: 0.2	10-64 y: 13.2	10-64 y: 17.5
≥ 65 y: 0.2	65-89 y: 4.1	≥ 65 y: 30.4	65-89 y: 34.8
	≥ 90 y: 4.1		≥80 y: 40.0

N/A: not applicable; N/R: not reported (or insufficiently clear to represent here); IPD: invasive pneumococcal disease; AOM: acute otitis media.

Table 1. Study overview on published economic evaluations of 10-valent and 13-valent pneumococcal conjugate vaccines (1st January 2006-31st January 2014)

Study	Country	Funding body	Study type	Perspective	Vaccine protection period (yrs)	Vaccine coverage (%)	Herd effect considered (Y/N)	Serotype replacement	Time horizon (yrs)	Discount rate (%)
O'Brien, 2009	US	None	CUA	Societal	N/R	N/R	N	Not considered	Lifetime	C:3, B:3
Chuck, 2010	Canada	Wyeth	CUA	Healthcare	N/R	83.8	Y (IPD only)	Not considered	1	N/A
Rozenbaum, 2010	The Netherlands	Wyeth	CEA, CUA	Healthcare, societal	5	N/R	Y (IPD only)	Reduced herd effect estimate	5	C:4, B:1.5
Rubin, 2010	US	Pfizer	CUA	Societal	5	90	Y	Post-PCV7 ecologic data as a way to inherently account for SR	10	C:3, B:3
Tablird, 2010	Canada, Germany, Mexico, Norway	GSK	CEA, CUA	Societal	N/R	80-91	Y	Net indirect effect (herd protection minus SR)	1	N/A
Kim, 2010	The Gambia	partially by Bill and Melinda Gates Foundation	CEA	Societal	5	90	N	Increase disease incidence	5	C:3, B:4
Sartori, 2010	Brazil	Ministry of Health of Brazil and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)	CEA	Healthcare, societal	2 (Pneumonia & AOM); 5 (IPD)	80-90 (1 st and 2 nd yr); 95 (3 rd yr on); 95 (3 rd yr on);	N	Not considered	25	C:3, B:3
Robberstad, 2011	Norway	GSK	CEA, CUA	Societal	9	95 (1 st yr); 90 (2 nd yr on); 80 (3 rd yr on);	Y (IPD only)	Net indirect effect (herd protection minus SR)	Lifetime	C:4, B:4
Newall, 2011	Australia	GSK	CUA	Healthcare	10	75 (1 st yr); 93 (2 nd yr on); 95 (3 rd yr on);	Y	Increase disease incidence	100	C:5, B:5
Tyo, 2011	Singapore	Ministry of Health	CUA	Healthcare	N/R	95	Y	Reduced herd effect estimate	5	C:3, B:3

Unueña, 2011	Argentina	Wyeth	CEA	Healthcare, societal	N/R	96.6(1st dose); 94.1(2nd dose); 91.6(3rd dose);	N	Reduced herd effect estimate	20	C.3, B.3
Diez-Domingo, 2011	Spain	Pfizer	CEA, CUA	Healthcare	6	95	Y	Increase disease incidence	Lifetime	C.3, B.3
Nakamura, 2011	77 middle-income countries	GAVI Alliance	CEA	Societal	5	Assumed to be same as for 3 doses of DTP-3	Y	Increase disease incidence	Lifetime	C.3, B.3
Krieger, 2012	Canada & UK	GSK	CEA, CUA	Healthcare, societal	10	100	Y(IPD only)	Net indirect effect (herd protection minus SR)	Lifetime	UK: C.3, B.3 Canada: C.3.5, B.3.5
Earnshaw, 2012	Canada	Pfizer	CUA	Healthcare	N/R	N/R	Y	Not consider	Lifetime	N/R
Sebeche By , 2012	Sweden	GSK	CUA	Societal	10	100	Y(IPD only)	Net indirect effect (herd protection minus SR)	Lifetime	C.3, B.3
Castaneda-Ojuela, 2012	Colombia	Ministry of Health of Colombia and the Colombian Expanded Program of Immunization,	CEA	Societal	N/R	90	N	Not considered	Lifetime	C.3, B.3
Strutton, 2012	Germany, Greece, the Netherlands	Wyeth	CEA, CUA	Healthcare	N/R	80-95	Y	Post-PCV7 ecologic data as a way to inherently account for SR	1	N/A
Blank, 2012	Switzerland	Pfizer	CEA, CUA	Healthcare	5	83	N	Not considered	10	C.3, B.3
Wu, 2012	Taiwan	National Science Council	CEA	Healthcare, societal	5	90	Y	Not considered	10	C.3, B.3
Van Hoek, 2012	England	The UK Department of Health Policy Research Programme	CUA	Healthcare	10	N/R	Y	Direct estimation using TDM	30	C.3.5, B.3.5
Bakir, 2012	Turkey	GSK	CUA	Healthcare	10	84	N	Not considered	1	N/A
Kick, 2013	Denmark, Sweden	Pfizer	CEA, CUA	Healthcare	N/R	N/R	Y	Post-PCV7 ecologic data as a way to	1	C.3, B.3

								inherently account for SR		
Kulipeng, 2013	Thailand	The Thai Health Promotion Foundation	CUA	Societal	5	99	Y	Vary serotype coverage parameter	Lifetime	C:3, B:3
Hoshi, 2013	Japan	The Ministry of Health, Labour and Welfare	CEA, CUA	Societal	N/R	76.1	Y	Net indirect effect (herd protection minus SR)	5	C:3, B:3
Ayiko, 2013	Kenya	GAVI Alliance	CEA	Societal	N/R	100	N	Increase disease incidence	N/R	C:3, B:3
Gomez, 2013	Peru	GSK	CEA, CUA	Healthcare	9	95 (PCV10, PCV13) 83 (PCV7)	N	Not considered	Lifetime	C:3.5, B:3.5
Lee, 2013	Hong Kong	GSK	CEA, CUA	Healthcare	10	100	Y	Not considered	10	C:5, B:5

Table 2. Main assumptions and results of economic evaluations on PCV10 and/or PCV13 (1st January 2006– 31st January 2014)

First author, country, year	Funding body	Vaccination costs per dose schedule	Model	Main effectiveness assumptions	Results
O'Brien, US, 2009	None	PCV7=US\$80 PCV11=US\$123 3+1 schedule	Markov model	Effectiveness versus AOM, PCV11 vs. PCV7: 1. 4-24 months: 28% vs. 6.4% 2. 25-36 months: 14% vs. 3.2% 3. 37-48 months: 7% vs. 1.6% IPD and pneumonia effectiveness as for PCV7 in Lieu et al, 2000 97.4% against additional serotypes (no cross protection) 3% or 5% for AOM with NTHI Herd effect: 2-4 y: 0.401; 5-9 y: 0.187; 10-14 y: 0.687; 15-19 y: 0.936 20-39 y: 0.736; 40-64 y: 0.634; 65+ y: 0.495 (Ratio of incidence pre-(2000-2002) vs. post-(2003-2008) PCV-7)	Cost-saving with savings from AOM outweighing savings from other pneumococcal disease (includes indirect costs of parental time and QALY losses of parents)
Chuck, Alberta, 2010	Wyeth	PCV7=PCV10=PCV13 = US\$74 3+1 schedule	Steady-state population model	97.4% against additional serotypes (no cross protection) No effect on NTHI AOM Pneumonia and AOM estimates: same as PCV7 (adjusted for additional IPD serotypes) Net herd effects of PCV10 = PCV13 = 10%	PCV13 dominates PCV10 (but reversed if effectiveness against NTHI AOM is included)
Rozenbaum, the Netherlands, 2010	Wyeth	PCV7 = US\$72.6 PCV10=US\$90.4 PCV13 = US\$108.3 3+1 schedule	Decision analysis model	94% against IPD additional serotypes (no cross protection) 7.3% against suspected pneumonia 12.9-22% against hospitalized pneumonia 4-6.7% against all cause AOM (Fin OM and KCP) 6-10% against complex AOM	PCV10 vs. PCV7: US\$76,035 per QALY gained PCV13 vs. PCV7: US\$71,863 per QALY gained
Rubin, US, 2010	Pfizer	PCV7 = US\$94.6 PCV13 = US\$115.9 3+1 schedule	Markov state transition model	94% against IPD additional serotypes (no cross protection) 7.3% against suspected pneumonia 12.9-22% against hospitalized pneumonia 4-6.7% against all cause AOM (Fin OM and KCP) 6-10% against complex AOM	PCV13 vs. PCV7: cost saving Catch up 16-23m: US\$3,714 per QALY gained Catch up 16-35m: US\$27,374 per QALY gained Catch up 16-59m: US\$80,385 per QALY gained
Tablird, Canada, Germany, Mexico, and Norway, 2010	GSK	PCV7=PCV10 3+1 schedule 2+1 schedule Country dependent	Steady-state population model	IPD schedule effectiveness and serotype specific effectiveness (based on Whitney15 including cross protection (6A, 19A) + 94% against additional PCV10 serotypes). Herd immunity for IPD (PCV10=PCV7): 1. < 5years: 15.4% 2. ≥ 5years: 29% All-cause pneumonia: 3. Hospitalized: 25.0% vs. 20.5% (PCV10 vs. PCV7) 4. Non-hospitalized: 4.3% (PCV10=PCV7) AOM due to VT: 57.6% vs. 57.2% (PCV10 vs. PCV7)	PCV10 vs. PCV7: cost-saving

				<p>AOM due to NTHi: -11% vs. +35.6% (PCV10 vs. PCV7)</p> <p>All-cause AOM: 6.7% vs. 22.9% (PCV10 vs. PCV7)</p> <p>All-cause primary endpoint pneumonia:</p> <ol style="list-style-type: none"> 1. PCV7: 26% 2. PCV10: 35% 3. PCV13: 41% <p>Pneumococcal meningitis/sepsis:</p> <ol style="list-style-type: none"> 4. PCV7: 16% 5. PCV10: 22% 6. PCV13: 26% <p>AOM impact excluded</p> <p>Herd immunity, serotype replacement explored in sensitivity analysis</p>	
Kim, the Gambia, 2010	partially by Bill and Melinda Gates Foundation	PCV7= PCV10=PCV13= US\$4.4 2+1 schedule	Markov cohort model		<p>All PCVs considered cost-effective (PCV7 / PCV10 / PCV13 vs. No vaccination): US\$994 / US\$732 / US\$557 (costs per DALY averted < 3xGDP/capita)</p> <p>PCV13 more cost-effective than PCV10, and PCV7</p>
Sartori, Brazil, 2010	Ministry of Health of Brazil and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)	PCV10=US\$19.6 3+1 schedule	ProVac model (25 cohort model)	<p>PCV10 effectiveness (no cross protection):</p> <ol style="list-style-type: none"> 1. IPD: 0-2 y: 94.0%; 2-5 y: 94.0%; 2. All-cause pneumonia (due to VT): 0-2 y: 87.5%; 2-5 y: 0%; 3. AOM (due to VT): all age groups: 0-2 y: 575%; 2-5 y: 0%; 	<p>Universal PCV10 vaccination vs. High-risk PCV10 vaccination: Cost-effective with US\$11.815 per DALY averted</p>
Robberstad, Norway, 2011	GSK	PCV7= PCV10=PCV13=US\$64.8 2+1 schedule	Markov cohort model	<p>IPD (all vaccine serotypes):</p> <ol style="list-style-type: none"> 1. PCV7: 94.7% 2. PCV10: 94.7% 3. PCV13: 94.7% <p>Non-invasive hospitalized pneumonia:</p> <ol style="list-style-type: none"> 4. PCV7: 17.7% 5. PCV10: 21.3% 6. PCV13: 22.2% <p>AOM due to VT (PCV7 / PCV10 / PCV13): 57.2 / 57.6 / 57.6; AOM replacement non-VT (PCV7 / PCV10 / PCV13): -33 / -33 / -33; AOM net NTHi efficacy (PCV7 / PCV10 / PCV13): -11 / 35.6 / -11;</p> <p>Myringotomy procedure (PCV7 / PCV10 / PCV13): 19.2 / 65.8 / 32.2</p>	<p>Both PCV13 and PCV10 dominates PCV7</p> <p>PCV10 vs. PCV13: Dominant (in terms of QALY)</p> <p>PCV10 vs. PCV13: US\$533 (in terms of LY)</p>

Newell, Australia, 2011	GSK	PCV7/2+1 schedule)=PCV10/3+1 schedule)=PCV13/2+1 schedule)= \$302.6	Markov state transition model	IPD (due to VT) (<5 yr) (no cross protection assumed): 1. PCV7: 2. PCV10: 4.8% 3. PCV13: 61% Non-invasive hospitalized pneumonia (<5 yr): 4. PCV10 and PCV13 assumed to be equal to PCV7 AOM (<5 yr): 5. PCV7: 6.6% 6. PCV10: 6.61% / 17.1% against NTHI AOM 7. PCV13: 8.1%	PCV13 vs. No vaccination: US\$61,595 per QALY gained PCV10 vs. No vaccination: US\$55,920 per QALY gained PCV7 vs. No vaccination: US\$72,295 per QALY gained
T'yo, Singapore, 2011	Ministry of Health	PCV7=US\$126.8; PCV10=PCV13=US\$134.4 2+1 schedule	Markov state transition model	IPD (by herd protection): 1. PCV7: 77.0% / 15.4% 2. PCV10: 78.1% / 15.6% 3. PCV13: 89.4% / 17.9% All-cause pneumonia (by herd protection): 4. PCV7: 5.6% / 1.1% 5. PCV10: 5.6% / 1.1% 6. PCV13: 6.5% / 1.3% AOM: 7. PCV7: 5.9% 8. PCV10: 6.0% 9. PCV13: 6.9%	PCV13 vs. No vaccination: US\$39,936 per QALY gained PCV10 vs. No vaccination: US\$47,846 per QALY gained PCV7 vs. No vaccination: US\$45,911 per QALY gained
Uruelfa, Argentina, 2011	Wyeth	PCV13=PCV10=US\$23.4 3+1 schedule	Markov cohort model	IPD (bacteremia, sepsis and meningitis) / serotype coverage: 1. PCV10: 97.4% / 74.6% 2. PCV13: 97.4% / 85.3% All-cause pneumonia: 3. PCV10: 30.3% 4. PCV10: 30.3% AOM: 5. PCV10: 33.6% 6. PCV13: 7.0%	PCV13 vs. No vaccination (payer): US\$11,614 per DALY averted PCV13 vs. No vaccination (societal): US\$11,150 per DALY averted PCV10 vs. No vaccination (payer): US\$9,519 per DALY averted PCV10 vs. No vaccination (societal): US\$9,066 per DALY averted PCV13 vs. PCV10 (payer): US\$29,861 per DALY averted PCV13 vs. PCV10 (societal): US\$29,295 per DALY averted
Diez-Domingo, Spain, 2011	Pfizer	PCV13=US\$681 2+1 schedule	Markov cohort model	PCV13 serotype coverage 1. IPD: < 5 y: 84%; >5 y: 64 2. Hospitalized pneumonia: <5 y: 49%; 5-17 y: 31%; >18 y: 37% 3. Community treated pneumonia: <5 y: 39%; 5-17 y: 21%; >18 y: 27% 4. Complex & simple AOM: <5 y: 18%; >5 y: 0%	PCV13 vs. No vaccination: US\$18,066 per LY gained PCV13 vs. No vaccination: US\$14,694 per DALY gained

Nakamura, 77 middle income countries, 2011	GAVI Alliance	PCV7=PCV13=PCV10=US\$19 (Lower-middle income countries) US\$12.7 (Upper middle income countries) US\$25.3 3 schedule	Decision analysis model	<p>< 5 yrs</p> <p>Serotype coverage (Africa, Asia, Europe, Latin America, Oceania): Pneumococcal pneumonia/ pneumococcal meningitis/ NPNM IPD</p> <p>1. PCV7: 0.487, 0.515, 0.716, 0.579, 0.582 2. PCV10: 0.719, 0.697, 0.807, 0.773, 0.748 3. PCV13: 0.769, 0.737, 0.881, 0.824, 0.791</p> <p>Vaccine efficacy against vaccine-type disease (PCV7=PCV10=PCV13):</p> <p>4. Pneumococcal pneumonia: 0.85 5. Pneumococcal meningitis: 0.85 6. NPNM IPD: 0.95</p> <p>Herd protection (PCV7=PCV10=PCV13):</p> <p>7. Pneumococcal pneumonia: 0.015 8. Pneumococcal meningitis: 0.028 9. NPNM IPD: 0.029</p> <p>Serotype replacement (PCV7=PCV10=PCV13):</p> <p>10. Pneumococcal pneumonia: 0.038 11. Pneumococcal meningitis: 0.038 12. NPNM IPD: 0.038</p> <p>> 5 yrs and adults</p> <p>Serotype coverage (Northern Africa, sub-Saharan Africa, Asia, Europe, Latin America, Oceania): Clinical pneumonia/ pneumococcal meningitis/ NPNM IPD</p> <p>13. PCV7: 0.36, 0.40, 0.33, 0.38, 0.31, 0.51 14. PCV10: 0.75, 0.56, 0.62, 0.56, 0.41, 0.59 15. PCV13: 0.93, 0.71, 0.79, 0.71, 0.63, 0.69</p> <p>Herd protection (PCV7=PCV10=PCV13): 5-14y, 15-44y, 45-69y, ≥70y</p> <p>16. Clinical pneumonia: 0.018, 0.026, 0.019, 0.015 17. Pneumococcal meningitis: 0.008, 0.056, 0.051, 0.056 18. NPNM IPD: 0.063, 0.065, 0.065, 0.065</p> <p>Serotype replacement (PCV7=PCV10=PCV13): 5-14y, 15-44y, 45-69y, ≥70y</p> <p>19. Clinical pneumonia: 0.096, 0.044, 0.097, 0.046 20. Pneumococcal meningitis: 0.096, 0.044, 0.097, 0.046 21. NPNM IPD: 0.096, 0.044, 0.097, 0.046</p>	<p>All middle-income countries (n=77): PCV7 vs. No vaccination: US\$2,026 per DALY averted PCV10 vs. No vaccination: US\$1,266 per DALY averted PCV13 vs. No vaccination: US\$1,140 per DALY averted</p> <p>Lower middle-income countries (n=42): PCV7 vs. No vaccination: US\$1,900 per DALY averted PCV10 vs. No vaccination: US\$1,165 per DALY averted PCV13 vs. No vaccination: US\$1,013 per DALY averted</p> <p>Upper middle-income countries (n=35): PCV7 vs. No vaccination: US\$2,406 per DALY averted PCV10 vs. No vaccination: US\$1,646 per DALY averted PCV13 vs. No vaccination: US\$1,393 per DALY averted</p> <p>Based on CHOICE. PCV7: cost-effective for 72 countries PCV10 and PCV13: cost effective for all countries</p>
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				IPD: 1. PCV10: 94.7% for all 7 serotypes by PCV7 (Assuming cross protection: 6A: 76% and 19A: 26%) 2. PCV13: 94.7% NTHI IPD: 3. PCV10: 35.6% 4. PCV13: 0% Pneumonia (GP vs. hospitalized): 5. PCV10: 4.3% vs. 22.9% 6. PCV13: 4.3% vs. 24.7% AOM due to VT (PCV10 vs. PCV13): 57.6% vs. 57.6% AOM due to non-VT (PCV10 vs. PCV13): -33% vs. -33% AOM net NTHI efficacy (PCV10 vs. PCV13): 35.6% vs. 0%;	PCV10 dominates PCV13
Kreier, Canada and the UK, 2012	GSK	(Canada) PCV13=PCV10=US\$75.3 (UK) PCV13=PCV10=US\$54.7 3+1 schedule	Markov cohort model		
Earnshaw, Canada, 2012	Pfizer	PCV13=PCV10=US\$85 2+1 schedule	Markov cohort model	Serotype coverage (PCV13 vs. PCV10) 1. PCV13: 0-2 y: 61%; 2-4 y: 68%; 5-17 y: 26%; 18-64 y: 28%; 65+ y: 22% 2. PCV10: 0-2 y: 18%; 2-4 y: 23%; 5-17 y: 26%; 18-64 y: 28%; 65+ y: 22% IPD: 1. PCV10: 94.7% for all 7 serotypes by PCV7 (assuming cross protection: 6A: 76% and 19A: 26%) 2. PCV13: 94.7% Pneumonia (hospitalized vs. ambulatory visits): 3. PCV10: 22.9% vs. 4.3% 4. PCV13: 24.7% vs. 4.3% AOM due to VT (PCV10 vs. PCV13): 57.6% vs. 57.6% AOM due to non-VT (PCV10 vs. PCV13): -33% vs. -33% AOM net NTHI efficacy (PCV10 vs. PCV13): 35.6% vs. -11%;	PCV13 dominates PCV10
SebeckID, Sweden, 2012	GSK	PCV13=PCV10=US\$87.8 2+1 schedule	Markov cohort model		PCV10 dominates PCV13
				Pneumococcal meningitis: 1. PCV7 vs. PCV10 vs. PCV13: 63% vs. 74% vs. 83% Radiological pneumonia: 2. PCV7 vs. PCV10 vs. PCV13: 18% vs. 21% vs. 24% AOM: 3. PCV7 vs. PCV10 vs. PCV13: 6% vs. 34% vs. 9%	
Castañeda-Ojuela, Colombia, 2012	Ministry of Health of Colombia and the Colombian Expanded Program of Immunization.	PCV7= US\$15.3; PCV10=US\$16.2; PCV13=US\$17.9 2+1 schedule	Markov cohort model		PCV7 vs. No vaccination: Dominant PCV10 vs. No vaccination: US\$1,892 per LYG gained PCV13 vs. No vaccination: US\$9,801 per LYG gained

			<p>Bacteremia (PCV7/PCV10/PCV13)</p> <p>1. 0-2 y: 0.74/0.81/0.92; 0.79/0.87/0.95; 0.67/0.71/0.88</p> <p>2. 2-4 y: 0.57/0.84/0.84; 0.79/0.87/0.95; 0.68/0.91/0.95</p> <p>3. 5-9 y: 0.44/0.84/0.84; 0.48/0.79/0.91; 0.56/0.83/0.83</p> <p>4. 10-14 y: 0.44/0.84/0.84; 0.48/0.79/0.91; 0.56/0.83/0.83</p> <p>5. 15-17 y: 0.44/0.84/0.84; 0.59/0.72/0.80; 0.28/0.66/0.73</p> <p>6. 18-29 y: 0.39/0.57/0.72; 0.59/0.72/0.80; 0.28/0.66/0.73</p> <p>7. 30-44 y: 0.39/0.57/0.72; 0.49/0.58/0.74; 0.28/0.66/0.73</p> <p>8. 45-49 y: 0.39/0.57/0.72; 0.49/0.58/0.74; 0.43/0.59/0.76</p> <p>9. 50-59 y: 0.39/0.57/0.72; 0.50/0.61/0.76; 0.43/0.59/0.43</p> <p>10. 60-64 y: 0.39/0.57/0.72; 0.53/0.61/0.77; 0.43/0.59/0.76</p> <p>11. ≥65 y: 0.39/0.57/0.72; 0.53/0.61/0.77; 0.48/0.64/0.77</p> <p>Meningitis</p> <p>1. 0-2 y: 0.73/0.85/0.90; 0.79/0.87/0.95; 0.74/0.84/0.93</p> <p>2. 2-4 y: 0.53/0.85/0.90; 0.79/0.87/0.95; 0.67/0.78/0.83</p> <p>3. 5-9 y: 0.35/0.83/0.63; 0.48/0.79/0.91; 0.33/0.42/0.83</p> <p>4. 10-14 y: 0.35/0.83/0.63; 0.48/0.79/0.91; 0.13/0.25/0.38</p> <p>5. 15-17 y: 0.35/0.83/0.63; 0.59/0.72/0.80; 0.48/0.60/0.48</p> <p>6. 18-29 y: 0.39/0.57/0.72; 0.59/0.72/0.80; 0.48/0.60/0.48</p> <p>7. 30-44 y: 0.39/0.57/0.72; 0.49/0.58/0.74; 0.48/0.60/0.75</p> <p>8. 45-49 y: 0.39/0.57/0.72; 0.49/0.58/0.74; 0.45/0.57/0.74</p> <p>9. 50-59 y: 0.39/0.57/0.72; 0.50/0.61/0.76; 0.45/0.57/0.74</p> <p>10. 60-64 y: 0.39/0.57/0.72; 0.53/0.61/0.77; 0.45/0.57/0.74</p> <p>11. ≥65 y: 0.39/0.57/0.72; 0.53/0.61/0.77; 0.43/0.52/0.60</p> <p>Pneumonia and AQM:</p> <p>1. 0-2 y: 0.73/0.83/0.91; 0.79/0.87/0.95; 0.71/0.78/0.91</p> <p>2. 2-4 y: 0.53/0.85/0.91; 0.79/0.87/0.95; 0.68/0.85/0.89</p> <p>3. 5-9 y: 0.35/0.83/0.74; 0.48/0.79/0.91; 0.45/0.63/0.83</p> <p>4. 10-14 y: 0.35/0.83/0.74; 0.48/0.79/0.91; 0.35/0.54/0.61</p> <p>5. 15-17 y: 0.35/0.83/0.74; 0.59/0.72/0.80; 0.38/0.63/0.74</p> <p>6. 18-29 y: 0.39/0.57/0.72; 0.59/0.72/0.80; 0.38/0.63/0.74</p> <p>7. 30-44 y: 0.39/0.57/0.72; 0.49/0.58/0.74; 0.38/0.63/0.74</p> <p>8. 45-49 y: 0.39/0.57/0.72; 0.49/0.58/0.74; 0.44/0.58/0.75</p> <p>9. 50-59 y: 0.39/0.57/0.72; 0.50/0.61/0.76; 0.44/0.58/0.75</p> <p>10. 60-64 y: 0.39/0.57/0.72; 0.53/0.61/0.77; 0.44/0.58/0.75</p> <p>11. ≥65 y: 0.39/0.57/0.72; 0.53/0.61/0.77; 0.46/0.58/0.69</p>	
Strutton, Germany, Greece, and the Netherlands, 2012	Wyeth	<p>(Germany)</p> <p>PCV7=PCV13=US\$67.1;</p> <p>PCV10=US\$54.6</p> <p>(Greece)</p> <p>PCV7=US\$71.7;</p> <p>PCV10=US\$57.7;</p> <p>PCV13=US\$67.9</p> <p>(The Netherlands)</p> <p>PCV7=PCV10=US\$78.2;</p> <p>PCV13=US\$83.9</p>	Markov cohort model	<p>PCV13 dominates PCV10 in all 3 countries</p>

Blank, Switzerland, 2012.	Pfizer	PCV7=US\$14.4; PCV13=US\$16.7 2+1 schedule	Decision analysis model	<p>Direct effect due to PCV13</p> <p>1. IPD: <1 y: 41%; 1-2 y: 75%;</p> <p>2. Hospitalized pneumonia: <1 y: 9%; 1-2 y: 16%;</p> <p>3. Non-hospitalized pneumonia: <1 y: 9%; 1-2 y: 16%;</p> <p>4. Complex AOM: <1 y: 10%; 1-2 y: 19%;</p> <p>5. Simple AOM: <1 y: 10%; 1-2 y: 19%;</p> <p>It was assumed that non-IPD direct effect PCV13 = direct effect PCV7*(1+serotype coverage of PCV13/serotype coverage of PCV7)</p>	PCV13 vs. PCV7: Cost-saving PCV13 with catch-up program vs. PCV7: Cost-saving
Wu, Taiwan, 2012	National Science Council	PCV13=US\$103.3 3+1 schedule	Transmission dynamic model	<p>PCV13 efficacy (adjusted for serotype distribution)</p> <p>1. Pneumococcal meningitis & bacteremia: 77.5%</p> <p>2. All-cause hospitalized pneumonia: 32.4%</p> <p>3. AOM: 8.9%</p>	PCV13 vs. No vaccination: Cost-effective with US\$18,847 per LY gained (< 3xGDP/capita Taiwan)
Van Hoek, England, 2012	The UK Department of Health Policy Research Programme	PCV13=US\$44.7 2+1 schedule	Transmission dynamic model	<p>PCV13 efficacy (adjusted for serotype distribution)</p> <p>1. Pneumococcal meningitis & bacteremia: 77.5%</p> <p>2. All-cause hospitalized pneumonia: 32.4%</p> <p>3. AOM: 8.9%</p>	PCV13 vs. Discontinuing PCV7 (with non-invasive outcome): 100% cost-effective based on PSA at the threshold of US\$47,607 per QALY gained PCV13 vs. Discontinuing PCV7 (without non-invasive outcome): 53% cost-effective based on PSA at the threshold of US\$47,607 per QALY gained
Bakır, Turkey, 2012	GSK	PCV7=PCV10=PCV13=US\$30.9 3+1 schedule	Decision analysis model	<p>1. IPD: PCV13=PCV10=PCV7 (shared serotypes)</p> <p>PCV13=PCV10=PCV7 (additional serotypes)=94.7%</p> <p>PCV10=PCV7 (serotype 6A)=76%</p> <p>2. NTHI-related IPD: PCV10=35.6%; PCV13=PCV7=0%</p> <p>3. Outpatient all-cause pneumonia: PCV13=PCV10=PCV7=4.3%</p> <p>4. Hospitalized all-cause pneumonia: PCV13=24.7%; PCV10=22.9%; PCV7=17.7%</p> <p>5. AOM due to VT: PCV13=PCV10=57.6%</p> <p>6. NTHI-related AOM: PCV10=35.3%</p> <p>7. AOM due to non-VT: PCV13=PCV10=PCV7=33%</p>	PCV10 vs. PCV7: Cost-saving PCV13 vs. PCV7: Cost-saving PCV10 vs. PCV13: Cost-saving
				<p>1. Serotype coverage PCV10 / PCV13: pneumococcal meningitis = pneumococcal bacteremia: 0.25-0.74 / 0.45-0.83 (Denmark); 0.25-0.48 / 0.63-0.66 (Sweden);</p> <p>2. Vaccine effectiveness PCV10 / PCV13: pneumococcal meningitis = pneumococcal bacteremia: 0.94 / 0.94 (Denmark and Sweden)</p> <p>inpatient pneumonia: 0.14 / 0.25 (Denmark); 0.08 / 0.20 (Sweden);</p> <p>outpatient pneumonia: 0.03 / 0.06 (Denmark); 0.02 / 0.05 (Sweden);</p> <p>mild AOM: 0.05 / 0.09 (Denmark); 0.02 / 0.05 (Sweden);</p> <p>moderate or severe AOM: 0.11 / 0.18 (Denmark); 0.05 / 0.12 (Sweden);</p>	
Klok, Denmark, and Sweden, 2013	Pfizer	PCV10=PCV13=US\$82.9 3+1 schedule	Markov state transition model		(Denmark) PCV13 vs. PCV10: Cost-saving (Sweden) PCV13 vs. PCV10: Cost-saving

Kulpeng, Thailand, 2013	The Thai Health Promotion Foundation	PCV10=US\$61.9 PCV13=US\$46.2 2+1 schedule	Markov model	<p>1. PCV13=PCV10=PCV7 (shared serotypes): 1PD: 89%; pneumonia:6%; AOM: 6%</p> <p>2. Serotype coverage: PCV7: <5y: 67.6%; >5y:38.09 / PCV10: <5y: 70.6%; >5y:43.71 / PCV13: <5y: 86.8%; >5y:60.19%</p> <p>3. Herd effect on 1PD: 20-39y:40%, 40-64y:14%,>65y:29%</p>	<p>PCV10 vs. No vaccination: US\$45,163 per QALY gained (without herd effect)</p> <p>PCV13 vs. No vaccination: US\$49,220 per QALY gained (without herd effect)</p> <p>PCV10 vs. No vaccination: US\$177,173 per QALY gained (with herd effect)</p> <p>PCV13 vs. No vaccination: US\$177,437 per QALY gained (with herd effect)</p>
Hoshi, Japan, 2013	The Ministry of Health, Labour and Welfare	PCV7 = US\$125 PCV13 = US\$162.5 3+1 schedule	Markov model	<p>1. 1PD: PCV13=PCV7 (shared serotypes): <1y:80%; 1-2y:80%; 2-3y:77.6%; 3-4y:75.3%; 4-5y: 73%</p> <p>2. AOM: PCV13=PCV7 (shared serotypes): <1y:54%; 1-2y:54%; 2-3y:51.2%; 3-4y:50.8%; 4-5y:48.3%</p> <p>3. hospitalized all-cause pneumonia: <1y:27%; 1-2y:27%; 2-3y:26.2%; 3-4y:25.4%; 4-5y: 24.6%</p>	<p>Base-case A (No extra protection against AOM compared to PCV7): PCV13 vs. PCV7: US\$471,536 vs. US\$444,850 per QALY (Payer vs. Societal perspective)</p> <p>Base-case B (No extra protection against AOM compared to PCV7): PCV13 vs. PCV7: US\$4,298 vs. cost-saving per QALY (Payer vs. Societal perspective)</p>
Ayeko, Kenya, 2013	GAHI Alliance	PCV 10 = US\$3.80 3 schedule	Decision analysis model	<p>Vaccine efficacy</p> <p>PCV10=PCV13=PCV7</p> <p>1. Meningitis/sepsis: PCV7=92%</p> <p>2. Bacteraemic and non-bacteraemic pneumonia: PCV7=77% (1) and (2) multiply with number of cases estimated to have disease caused by serotypes contained in PCV10 and 13 and multiply with immunization coverage</p> <p>Herd effect and serotype replacement explored in sensitivity analysis</p>	<p>PCV10 vs. no vaccine: US\$ 65 per DALY averted, US\$ 328 per case averted, US\$ 2,140 per death averted</p> <p>PCV13 vs. no vaccine: US\$ 51 per DALY averted, US\$ 260 per case averted, US\$ 1,702 per death averted</p>
Gomez, Peru, 2013	GSK	PCV7 = US\$21.9 PCV10 = US\$14.7 PCV13 = US\$16.8 2+1 schedule	Markov model	<p>Vaccine efficacy</p> <p>1. 1PD: PCV13=PCV10=PCV7=94.7%</p> <p>2. NTH-associated ID: PCV10=35.3%=against NTH-associated AOM</p> <p>3. CAP: PCV13=PCV10=PCV7=23.4% (hospitalized all-cause pneumonia), 7.3% (all-cause ambulatory pneumonia)</p> <p>4. AOM: PCV13=PCV10=PCV7=56%/33% (serotype replacement effect)</p> <p>5. NTH AOM: PCV10=35.3%; PCV7=PCV13= -11%</p> <p>6. Coverage on pneumococcal type in AOM: PCV7=69.8%; PCV10=76.2%; PCV13=89.5%</p> <p>Herd effect was explored in scenario analysis</p>	<p>PCV7 vs. no vaccine: US\$6,194 per QALY gained</p> <p>PCV10 vs. no vaccine: US\$5487 per QALY gained</p> <p>PCV13 vs. no vaccine: US\$4,635 per QALY gained</p> <p>PCV10 vs. PCV7: Dominated</p> <p>PCV13 vs. PCV10: -US\$2,808 per QALY gained</p> <p>PCV7 vs. no vaccine: US\$5,582 per LY gained</p> <p>PCV10 vs. no vaccine: US\$4,293 per LY gained</p> <p>PCV13 vs. no vaccine: US\$5,004 per LY gained</p> <p>PCV10 vs. PCV7: -US\$3000 per LY gained</p> <p>PCV13 vs. PCV10: US\$170,391 per LY gained</p> <p>PCV10 dominant vs PCV 13 and PCV7</p>

Lee, Hong Kong, 2013	GSK	PCV10 = PCV 13 = USD 27.5 3+1 schedule	Markov model	<p>Vaccine efficacy</p> <ol style="list-style-type: none"> 1. IPD: PCV10 (serotypes 1, 5, 7F) = PCV 13 (serotypes 1, 3, 5, 6A, 7F, 19A) = 94.7%; PCV10 (serotype 6A) = 76.0% 2. Hospitalized pneumonia: PCV10 = 23.4%; PCV 13 = 28.2% 3. Pneumonia (GP visit): PCV 10 = 4.3%; PCV 13 = 7.95% 4. NTHI AOM (GP visit): PCV 10 = PCV 13 = 0% 5. Reduction of myringotomy: PCV 10 = 23%; PCV 13 = 29.6% 6. Herd effect: PCV 13 = 15.4% children younger than 5 years, 29.0% children older than 5 years 	<p>HKD 6,115,185 per LY gained</p> <p>PCV 10 dominant vs. PCV 13 in cost per QALY gained (-HKD 379,265 per QALY gained)</p>
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* All costs were adjusted to values of 2013 based on Consumer Price Indices and exchange rates

Table 3. Sensitivity analyses, threshold analyses and scenario analyses conducted by each study on PCV13 and/or PCV10 (1st January 2006- 31st January 2014)

First author, country, year	1-way	2-way	PSA	Threshold	CEAC	Scenario
O'Brien, US, 2009	Yes	Yes	-	Yes	-	-
Chuck, Alberta, 2010	-	-	Yes	-	-	-
Rozenbaum, the Netherlands, 2010	Yes	-	Yes	Yes	Yes	Yes
Rubin, US, 2010	-	-	-	-	-	-
Talbird, Canada, Germany, Mexico, and Norway, 2010	Yes	-	-	Yes	-	-
Kim, the Gambia, 2010	Yes	-	Yes	-	Yes	Yes
Sartori, Brazil, 2010	Yes	-	-	Yes	-	Yes
Robberstad, Norway, 2011	Yes	Yes	Yes	-	Yes	Yes
Newall, Australia, 2011	Yes	-	Yes	-	Yes	Yes
Tyo, Singapore, 2011	Yes	-	-	-	-	Yes
Urueña, Argentina, 2011	Yes	-	-	-	-	Yes
Diez-Domingo, Spain, 2011	Yes	-	-	-	-	Yes
Nakamura, 77 middle-income countries, 2011	Yes	-	-	-	-	-
Krøner, Canada, and the UK, 2012	Yes	-	Yes	-	-	-
Earnshaw, Canada, 2012	Yes	-	-	Yes	-	Yes
Sebeche ^{SE} , Sweden, 2012	Yes	-	-	-	-	Yes
Castafieda-Ojuela, Colombia, 2012	Yes	-	Yes	-	Yes	Yes
Strutton, Germany, Greece, and the Netherlands, 2012	Yes	-	-	-	-	Yes
Blank, Switzerland, 2012	Yes	-	-	-	-	-
Wu, Taiwan, 2012	Yes	-	Yes	-	Yes	-
Van Hoek, England, 2012	-	-	Yes	Yes	Yes	Yes
Bakir, Turkey, 2012	Yes	-	Yes	-	-	-
Kick, Denmark and Sweden, 2013	Yes	-	-	-	-	Yes
Kulpeng, Thailand, 2013	-	-	-	-	-	-
Hoshi, Japan, 2013	Yes	-	Yes	Yes	Yes	Yes
Ayiko, Kenya, 2013	-	-	Yes	-	-	-
Gomez, Peru, 2013	Yes	-	Yes	-	-	Yes
Lee, Hong Kong, 2013	Yes	Yes	Yes	-	-	Yes

Table 4. Influential parameters for each study

Study	Vaccine price	Cost of disease	Cost of long-term sequelae	Vaccine efficacy	Disease Incidence	Mortality of IPD & pneumonia	Vaccine waning	Dose regimen	Indirect cost	Herd effect	Utility	discount rate
O'Brien, US, 2009									✓			
Chuck, Alberta, 2010												
Rozenbaum, the Netherlands, 2010												
Rubin, US, 2010										✓		
Talbird, Canada, Germany, Mexico, and Norway, 2010			✓				✓			assumed equal between countries		
Kim, the Gambia, 2010	✓			✓		✓						✓
Sartori, Brazil, 2010	✓				✓							
Robberstad, Norway, 2011					✓ (reduction rate on myringotomy, GP for AOM)						✓	
Newell, Australia, 2011	✓			✓	✓					✓		
Tyo, Singapore, 2011	✓			✓						✓		
Urueña, Argentina, 2011	✓				✓ (by varying disease incidence)	✓				✓		✓
Díaz-Domingo, Spain, 2011	✓	✓					✓	✓		✓		
Nakanura, 77 middle-income countries, 2011	✓			✓ (serotype coverage)	✓							
Krieger, Canada, and the UK, 2012		✓		✓								
Earnshaw, Canada, 2012						✓		✓	✓	✓		
Seebeck-Bj, Sweden, 2012		✓		✓	✓						✓	

Castañeda-Orjuela, Colombia, 2012					✓						✓		
Stutton, Germany, Greece, and the Netherlands, 2012	✓				✓		✓						✓
Blank, Switzerland, 2012	✓	✓					✓		✓		✓		
Wu, Taiwan, 2012	✓					✓					✓		
Van Hoek, England, 2012													
Bakir, Turkey, 2012													
Kick, Denmark and Sweden, 2013													
Kulpeng, Thailand, 2013						✓ (pneumonia)		✓			✓		✓
Hoshi, Japan, 2013	✓				✓				✓				
Ayeko, Kenya, 2013	✓						✓						
Gomez, Peru, 2013	✓				✓ (hospitalization CAP, AOM)								
Lee, Hong Kong, 2013				✓	✓ (AOM)						✓		

Figures

Figure 1 Flow diagram of the selection process to identify studies to be included (1st January 2006 – 31st January 2014)