

# Rapport coût-efficacité des vaccins antipneumococciques conjugués 10- valent et 13-valent chez l'enfant

*KCE reports 155B*

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Présentation : Le Centre fédéral d'expertise des soins de santé est un parastatal, créé le 24 décembre 2002 par la loi-programme (articles 262 à 266), sous tutelle du Ministre de la Santé publique et des Affaires sociales, qui est chargé de réaliser des études éclairant la décision politique dans le domaine des soins de santé et de l'assurance maladie.

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## KCE report I55B

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- Remerciements :** Les auteurs tiennent à remercier les personnes suivantes pour leur aide quant à l'obtention d'informations : Anne Kongs (Vlaams Agentschap Zorg en Gezondheid), Murielle Deguerry et Peter Verduyck (Observatoire de la santé et du social de Bruxelles-Capitale), Marie-Anne Goosse (Ministère de la Communauté Française).
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- Conflits d'intérêt :** Willy Peetermans a reçu des fonds pour la conduite de recherches ainsi que des indemnités de voyage pour participer à des congrès. Béatrice Swennen a reçu une rémunération pour une communication, un subside de formation, une prise en charge de frais de voyage ou un paiement à l'occasion d'une participation à un symposium. Yves Van Laethem a reçu des fonds pour la conduite de recherches ainsi que des honoraires de consultation de la part des firmes pharmaceutiques GSK et Wyeth/Pfizer. Il a en outre reçu des indemnités de voyage pour participer à des congrès. Iris Deschutter a reçu des fonds pour la conduite de recherches ainsi que des indemnités de voyage pour participer à des congrès de la part de GSK et Wyeth/Pfizer. David Tuerlinckx a reçu des honoraires de consultation ainsi que des indemnités de voyage pour participer à des congrès de la part de GSK et Wyeth/Pfizer. Anne Vergison a reçu des honoraires de consultation et d'orateur de GSK et Wyeth/Pfizer, ainsi que des fonds pour la conduite de recherches. Jan Verhaegen est membre des comités consultatifs de Pfizer et GSK et a reçu des indemnités de voyage de ces firmes afin de participer à des symposium. Martine Sabbe a été consultante externe non-rémunérée pour le comité consultatif de Wyeth/Pfizer au sujet de l'étude « Pneumococcal vaccination in the elderly population » in 2009. Pierre Van Damme a agi en tant que dirigeant et investigateur principal d'essais cliniques sur les vaccins pour l'Université d'Anvers.

L'Université d'Anvers a obtenu à ces fins des bourses de recherche provenant des producteurs de vaccins. Les honoraires perçus pour les présentations sur les vaccins ont tous été versés sur un fond d'éducation géré par l'Université d'Anvers. La chair scientifique "Evidence-Based Vaccinology" de l'Université d'Anvers a été fiancée durant la période 2009-2011 par un don provenant de Pfizer.

Disclaimer :

**Les experts externes ont été consultés sur une version (préliminaire) du rapport scientifique. Leurs remarques ont été discutées au cours des réunions. Ils ne sont pas co-auteurs du rapport scientifique et n'étaient pas nécessairement d'accord avec son contenu.**

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**Enfin, ce rapport a été approuvé à l'unanimité par le Conseil d'administration.**

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Mise en Page:

Ine Verhulst

Bruxelles, 30 mai 2011

Etude n°: 2009-52

Domaine: Health Technology Assessment (HTA)

MeSH: Vaccines, Conjugate; Pneumococcal vaccines; Infant; Pneumococcal Infections; Cost-Benefit Analysis

Classification NLM: WC 217

Langage: français, anglais

Format: Adobe® PDF™ (A4)

Dépôt légal: D/2011/10.273/20

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Comment citer ce rapport?

Beutels P, Blommaert A, Hanquet G, Bilcke J, Thiry N, Sabbe M, Verhaegen J, De Smet F, Callens M, Van Damme P. Rapport coût-efficacité des vaccins antipneumococques conjugués 10-valent et 13-valent chez l'enfant. Health Technology Assessment (HTA). Bruxelles: Centre fédéral d'expertise des soins de santé (KCE). 2011. Reports 155B. D/2011/10.273/20





## PRÉFACE

Bien qu'il porte le nom de *Streptococcus pneumoniae*, le pneumocoque (nom courant de cette bactérie) est aussi responsable de toute une série d'infections autres que les pneumonies. Et pas des moindres : méningites, bactériémies, chocs septiques... Par ailleurs, il peut être à l'origine d'autres infections, moins graves mais beaucoup plus fréquentes, comme les otites. Ce sont surtout les jeunes enfants de moins de deux ans et les personnes âgées qui constituent la population à risque. De nombreuses formes différentes du pneumocoque circulent – on parle de sérotypes – de sorte qu'un vaccin efficace doit en fait toujours combiner différents vaccins ciblant chacun différents sérotypes.

En 2006, le KCE a publié un premier rapport sur le vaccin disponible à ce moment là, qui protégeait contre 7 sérotypes (PCV7). Notre avis avait été plutôt positif mais nous avons pointé du doigt les nombreuses inconnues de l'analyse qui faisaient que les projections sur l'utilité future du vaccin présentaient une grande marge d'incertitude. Aujourd'hui, cinq ans plus tard, les autorités demandent de nous prononcer sur deux nouveaux vaccins, couvrant respectivement 10 et 13 sérotypes. Le Conseil Supérieur de la Santé s'est déjà prononcé prudemment en faveur du deuxième, ce qui semble logique a priori : plus un vaccin contient de sérotypes, meilleure devrait être la protection.

Mais les choses ne sont pas aussi simples. Ainsi, en l'occurrence, 13 ne semble pas égal à 10 plus 3. De plus nous sommes face à différents schémas de vaccination, différents prix et une série d'incertitudes. Sur quel prix pourra-t-on finalement compter? Les bénéfices prévus du PCV7 sont-ils confirmés? N'allons-nous pas faire face à l'émergence d'autres sérotypes? Et les questions ne s'arrêtent pas là.

C'est la raison pour laquelle, dans ce genre d'étude, les conclusions sont rarement noires ou blanches. Apporter le plus d'informations objectives possible aux décideurs, telle est l'ambition de ce rapport qui est le fruit d'une collaboration avec l'équipe universitaire d'Anvers. Nous la remercions pour son travail de qualité, ainsi que les nombreux autres experts sur qui nous avons pu compter pour nous éclairer.

Jean Pierre CLOSON  
Directeur général adjoint

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Directeur général

## Résumé

### INTRODUCTION

#### LES MALADIES À PNEUMOCOQUES

Le *Streptococcus pneumoniae* (ou “pneumocoque”) est une bactérie qui infecte les enfants et les adultes dans le monde entier. Il en existe plus de 90 sérotypes, qui diffèrent non seulement au niveau de leur structure mais aussi de la pathologie qu'ils peuvent induire ainsi que des groupes d'âge les plus touchés. Le *S. pneumoniae* constitue l'une des premières causes de méningite, de pneumonie et d'otite moyenne chez le jeune enfant, et représente également une cause de morbidité élevée chez les sujets âgés qui supportent la charge de mortalité la plus élevée. Les formes les plus graves des pathologies provoquées par le *S. pneumoniae* sont les maladies invasives dues au pneumocoque (invasive pneumococcal disease, IPD), à savoir la méningite et la bactériémie, qui peuvent provoquer un choc septique. Les IPD frappent les extrêmes des âges de la vie, à savoir les enfants en bas âge et les personnes âgées. Les pathologies non invasives, essentiellement la pneumonie et l'otite moyenne, sont d'ordinaire moins graves mais considérablement plus courantes que les IPD. L'otite moyenne est surtout diagnostiquée chez le jeune enfant tandis que la pneumonie frappe à tout âge. En dépit d'un accès adéquat aux soins et au traitement antibiotique, la mortalité et la morbidité dues aux IPD restent élevées de nos jours. Dans diverses régions du monde, le traitement des pathologies à pneumocoques se trouve confronté au problème de l'émergence d'une résistance à la pénicilline et aux autres antibiotiques.

En Belgique, la charge annuelle de la maladie due au *S. pneumoniae* au cours de la période de pré-vaccination (2005) était estimée à 1 403 cas d'IPD, y compris 96 méningites et 500 bactériémies. *S. pneumoniae* a été responsable de 53 décès, dont 12 imputables à une méningite. En outre, quelque 21 000 patients souffrant d'otite moyenne et 4 300 patients atteints de pneumonie ont consulté un médecin généraliste en 2004, et l'on estime que 30-50% de tous ces cas sont provoqués par le *S. pneumoniae*.

#### LA VACCINATION PCV7

Un premier vaccin antipneumococcique conjugué (PCV) a reçu sa licence en 2001 en Europe. Ce vaccin contient les antigènes de sept sérotypes (4, 6B, 9V, 14, 18C, 19F and 23F), que nous appellerons ici sérotypes vaccinaux.

Aux Etats-Unis, l'introduction de la vaccination PCV7 dans le plan de vaccination des enfants en bas âge avait entraîné une chute spectaculaire du nombre de cas d'IPD. De plus, un effet indirect de taille avait été observé, à savoir une diminution des IPD dans les groupes non vaccinés, en raison d'une baisse de la circulation des pathogènes suite à la vaccination massive des enfants. C'est ce que l'on appelle une « immunité de groupe ou collective ». En revanche, le PCV7 a également favorisé une hausse des IPD due aux sérotypes qui ne sont pas inclus dans le vaccin (ce que l'on appelle les sérotypes non vaccinaux) en vertu d'un « effet de remplacement ». Autrement dit, les sérotypes vaccinaux ont été remplacés par des sérotypes non vaccinaux.

En Belgique, les sept sérotypes du PCV7 étaient responsables de 72% des cas d'IPD chez les enfants <2 ans en 2002-03. Le PCV7 était recommandé en Belgique, mais n'est devenu disponible qu'en octobre 2004 en raison d'une pénurie de ce vaccin. Dans un premier temps, le PCV7 était recommandé pour les enfants de <2 ans, mais l'essentiel de son coût était supporté par les parents, la plupart des mutuelles l'ayant ensuite petit à petit remboursé en partie. En juin 2006, une étude du KCE a examiné l'efficacité réelle ainsi que le rapport coût-efficacité de la vaccination infantile en utilisant le vaccin PCV7. L'étude en question avait conclu que le rapport coût-efficacité de la vaccination infantile universelle avec le PCV7 n'était pas clair en raison des incertitudes associées aux effets de l'immunité de groupe et du remplacement des sérotypes. Le rapport avançait toutefois le raisonnement selon lequel l'incertitude en termes de rapport coût-efficacité



serait inférieure si l'on utilisait un schéma vaccinal 2+1 (2 doses à titre de série primaire et 1 rappel), plutôt que le schéma 3+1 préconisé à l'époque.

Dans la foulée de ce rapport, la Conférence interministérielle a décidé en juin 2006 d'introduire la vaccination infantile universelle avec le PCV7 en Belgique en utilisant un schéma 2+1, autrement dit une vaccination à 2, 4 et 12 mois. Cette décision a abouti à l'inclusion gratuite de ce vaccin dans les programmes régionaux de vaccination à compter de janvier 2007, avec une vaccination de rattrapage pour les enfants jusqu'à 2 ans. La couverture vaccinale du vaccin PCV7 a été estimée respectivement à 81 et 89% pour le schéma complet en Wallonie et en Flandre, en 2008-2009.

Après l'introduction du PCV7 en Belgique, malgré la couverture vaccinale élevée, l'incidence globale des IPD n'a affiché qu'une baisse modérée chez les enfants en bas âge (-37% à -46% chez les enfants de <2 ans en 2008 par comparaison avec 2002-03). Les données de la surveillance post-vaccination des IPD a montré un impact élevé et rapide sur les sérotypes vaccinaux dans tous les groupes d'âge pédiatriques, mais également une élévation concomitante des sérotypes non vaccinaux. Un tel constat a été posé pour les sérotypes 33F, 10A, 12F, 24F, et en particulier pour les sérotypes 1, 7F et 19A qui représentaient ensemble 55% des IPD en Belgique en 2008. Toutefois, le sérotype 19A avait déjà entamé sa progression en Belgique avant l'introduction du PCV7. En conséquence, on ne sait pas avec certitude dans quelle mesure cette progression est due au remplacement des sérotypes. Par ailleurs, d'autres facteurs, notamment les tendances temporelles naturelles et le recours aux antibiotiques, sont susceptibles de jouer un rôle également. On escomptait également une efficacité du PCV7 contre l'otite moyenne aiguë (OMA) et la pneumonie. Or, la surveillance de routine du réseau sentinelle flamand de médecins généralistes « Intego » n'a suggéré aucune preuve d'un impact visible. En outre, contrairement à l'expérience américaine, aucune immunité de groupe n'a pu être observée en Belgique sur la base des données disponibles, un constat qui s'inscrit dans le droit fil de ce que l'on observe dans la plupart des autres pays de l'UE.

## NOUVEAUX VACCINS ANTIPNEUMOCOCCIQUES CONJUGUÉS : PCV10 ET PCV13

Deux nouveaux vaccins antipneumococciques conjugués ont reçu l'autorisation de mise sur le marché de la Commission européenne en 2009. Ces vaccins couvrent les 7 sérotypes inclus dans le vaccin PCV7, de même que des sérotypes supplémentaires qui sont actuellement responsables d'une part élevée des maladies invasives.

Le Synflorix ou PCV10 (GSK) est un vaccin 10-valent qui contient les antigènes des sérotypes 1, 5 et 7F en plus de ceux du PCV7. Le fabricant allègue un effet protecteur élevé non seulement contre les OMA dues aux sérotypes pneumococciques, mais également contre celles qui sont imputables à *Haemophilus influenzae* non typable (HiNT) puisque la protéine porteuse du vaccin est dérivée d'*Haemophilus influenzae*. La question de savoir si le PCV10 pourrait apporter une protection contre le sérotype 19A, via une protection croisée (conférée par la réponse immunitaire contre le sérotype 19F qui appartient au même groupe), fait aussi débat.

Prevenar 13 ou PCV13 (Pfizer) est un vaccin 13-valent qui contient les antigènes des sérotypes 1, 3, 5, 6A, 7F et 19A en plus de ceux du PCV7.

## OBJECTIFS DE L'ÉTUDE

Face à l'augmentation exponentielle actuellement observée des sérotypes 1, 5 et 7F en Belgique et compte tenu de l'impact relativement faible de la vaccination PCV7, une transition du PCV7 vers les nouveaux vaccins PCV semble opportune puisque ces deux derniers couvrent ces sérotypes. Toutefois, il est ardu de déterminer lequel de ces deux vaccins doit recueillir la préférence. Le PCV10 pourrait apporter une protection accrue contre l'OMA, tandis que le PCV13 offre une plus vaste couverture des sérotypes responsables des IPD (certainement contre le sérotype 19A en pleine progression). Le choix entre ces vaccins doit également être posé dans un contexte d'incertitude à propos du remplacement des sérotypes à l'avenir (puisque d'autres sérotypes en progression ne sont pas couverts par les nouveaux vaccins) et en tenant compte du prix de chaque vaccin.

Compte tenu de la disponibilité de ces nouveaux vaccins, le présent rapport a pour but d'estimer l'efficacité réelle ainsi que le rapport coût-efficacité incrémentiel du remplacement du PCV7 par le PCV10 ou le PCV13 en Belgique, en tenant compte de l'immunité de groupe et du remplacement des sérotypes.

## PROTECTION CONFÉRÉE PAR LES NOUVEAUX VACCINS ANTIPNEUMOCOCCIQUES CONJUGUÉS

Dans le sillage du précédent rapport du KCE sur le PCV7, l'étude de la littérature visant à documenter ce chapitre a débuté le 1<sup>er</sup> janvier 2006 pour s'achever le 1<sup>er</sup> mars 2011. Il n'existe qu'un nombre limité de données relatives à l'efficacité clinique du PCV10 et du PCV13. En utilisant des corrélats de protection pour l'efficacité vaccinale, les études se sont plutôt concentrées sur les marqueurs indiquant une élévation de la réponse immunitaire (par sérotype), exprimée par concentrations d'anticorps et activité opsonophagocytaire (OPA). L'OPA mesure l'activité des anticorps et leur capacité à éliminer les pneumocoques et est dès lors considérée comme un meilleur marqueur de la protection clinique. Il n'y avait pas de données relatives à l'efficacité réelle de ces nouveaux vaccins.

### PCV10

Il a été établi que le PCV10 induit la formation d'anticorps contre tous les sérotypes pneumococciques présents dans le vaccin. Il a également été prouvé que le PCV10 n'était pas inférieur au PCV7 pour les 7 sérotypes dans un schéma 3+1. La réponse immunitaire aux sérotypes supplémentaires était élevée, en dépit du fait que les réponses OPA pour les sérotypes 1 et 5 soient inférieures aux réponses pour les sept autres sérotypes du vaccin PCV7. Certains éléments indiquaient par ailleurs que le PCV10 peut induire un certain degré de protection contre le sérotype 19A en progression, sur la base des réponses immunitaires.

Afin d'évaluer son efficacité contre l'OMA, un essai clinique a utilisé le vaccin précurseur du PCV10 (PCV11) qui est similaire au PCV10, si ce n'est qu'il contenait également l'antigène du sérotype 3. Dans cet essai, une protection de 34% contre l'OMA a été établie. L'étude a laissé entendre que le vaccin protège non seulement contre les sérotypes pneumococciques mais aussi contre l'*Haemophilus influenzae* non typable (HiNT).

### PCV13

Les essais avec le PCV13 ont établi que les réponses anticorps et les niveaux OPA associés au PCV13 n'étaient pas inférieurs à ceux du PCV7 pour les 7 sérotypes. Ces essais ont également montré qu'il existe des réponses immunitaires suffisantes pour les sérotypes supplémentaires, à l'exception du sérotype 3 qui présentait une réponse immunitaire inférieure. Aucun essai n'a évalué l'efficacité clinique du PCV13.

# EVALUATION ÉCONOMIQUE DU PCV10 ET DU PCV13

## REVUE DE LA LITTÉRATURE

Cette étude s'est limitée aux évaluations du PCV10 et/ou du PCV13 qui ont été publiées entre le premier janvier 2006 (la limite de recherche du précédent rapport du KCE) et le premier mars 2011. A l'exception d'une étude, aucune des 8 évaluations économiques publiées qui ont été identifiées n'avait intégré l'effet de l'immunité de groupe et du remplacement des sérotypes afin d'estimer le rapport coût-efficacité des PCV. La plupart des évaluations ont tendance à conclure que le PCV13 est plus coût-efficace que le PCV10. Une seule étude rapporte l'inverse, à savoir que le PCV10 est plus coût-efficace que le PCV13, si l'on part de l'hypothèse d'un effet du PCV10 sur l'OMA induite par le HiNT.

La plupart des évaluations économiques présentent d'importantes lacunes. D'abord, elles n'ont pas tenu compte des effets du remplacement des sérotypes et de l'immunité de groupe. Ensuite, elles n'ont pas effectué d'analyses de sensibilité sur le prix des vaccins, un paramètre pourtant très influent. Troisièmement, elles n'ont pas étudié l'impact de diverses hypothèses pour estimer l'efficacité réelle comparative des vaccins, alors que cette dernière revêt une importance cruciale en raison de la rareté des données cliniques sur le PCV10 et le PCV13.

Dans l'évaluation économique développée dans le cadre du projet actuel, nous réalisons des projections de l'impact du PCV10 et du PCV13 en tenant compte de ces aspects.

## RAPPORT COÛT-UTILITÉ DU PCV10 ET DU PCV13 EN BELGIQUE

### Description du modèle et hypothèses

Nous avons développé un modèle de simulation qui simule l'incidence et les conséquences des infections à pneumocoques dans des cohortes d'enfants vaccinés ainsi qu'au sein de la population en général. Afin de paramétrer ce modèle, nous avons utilisé des sources de données belges de même que la littérature internationale.

Ce modèle intègre les effets de l'immunité de groupe et du remplacement des sérotypes et tient également compte de la mesure dans laquelle le PCV10 : a) procure une protection supplémentaire contre l'OMA versus le PCV13 et b) apporte une certaine protection contre le sérotype 19A. L'efficacité vaccinale spécifique à chaque sérotype contre les IPD a été déduite indirectement des données immunologiques (anticorps et mesures OPA), et a été ajustée sur base des données d'observation de l'efficacité réelle du vaccin PCV7. L'effet du remplacement des sérotypes a été introduit dans le modèle en tant que réduction de la couverture des sérotypes pour les IPD, et en tant que réduction de l'efficacité vaccinale pour l'OMA et la pneumonie (puisque'il n'y a pas de données disponibles spécifiques au sérotype pour ces états pathologiques). Une telle méthode implique que le même paramètre pour le remplacement des sérotypes induira davantage de remplacement pour le PCV13 que pour le PCV10. Les hypothèses relatives à l'immunité de groupe, au remplacement des sérotypes, à la protection supplémentaire potentielle du PCV10 contre l'OMA et le sérotype 19A, de même que l'efficacité clinique, sont étudiées de manière fouillée dans les analyses des scénarios.

Les coûts directs des soins de santé ont été estimés sur la base d'une enquête nationale intensive en face-à-face. Les prix des vaccins PCV7, PCV10 et PCV13 ont été fixés à leur coût actuel en pharmacie, à savoir €66,15, €70,44 et €74,55 par dose, respectivement, mais ces valeurs ont été soumises à d'importantes variations dans le modèle de simulation (y compris une hypothèse d'égalité des prix).

Compte tenu du plan de vaccination infantile en routine et du fait que le PCV10 ne fasse actuellement l'objet d'une licence que pour un schéma 3+1, nous nous concentrons sur les options de vaccination suivantes : (1) la situation actuelle avec une vaccination PCV7 utilisant un schéma 2+1; (2) la vaccination PCV13 avec un schéma 2+1 ou un schéma 3+1; (3) la vaccination PCV10 avec un schéma 3+1. Un schéma 2+1 a également été étudié pour le PCV10, puisque l'on pourrait escompter des changements au niveau du schéma autorisé. Nous avons comparé les options 2 et 3 à l'option 1, de même que de manière incrémentielle l'une par rapport à l'autre.

## Résultats - PCV10 et PCV13 versus PCV7

En ayant recours à diverses hypothèses à propos des mesures de l'efficacité réelle des vaccins, des effets de l'immunité de groupe et du remplacement des sérotypes, les résultats ont montré de façon constante que les deux nouveaux vaccins sont très probablement susceptibles d'induire des économies ou d'être considérés comme coût-efficaces par rapport au PCV7, même à leur prix public actuel en pharmacie.

Si l'on exclut l'effet de l'immunité de groupe et qu'on les compare au PCV7, les nouveaux vaccins PCV10 et PCV13 permettraient d'éviter, tous scénarios confondus, 113 à 118 IPD, 181 à 236 pneumonies, 587 à 6 317 otites moyennes et un peu moins de deux décès. Le ratio coûts-efficacité différentiel du PCV10 (schéma 3+1) et du PCV13 (schéma 2+1) par rapport au PCV7 allait de la dominance (autrement dit, les nouveaux vaccins sont tous les deux plus efficaces et moins onéreux que le PCV7) à €12 400 par QALY (quality-adjusted life-year, années de vie ajustées pour la qualité) gagnée pour le PCV10 et le PCV13. Ces valeurs étaient plus favorables lorsque l'on partait du postulat d'effets liés à une immunité de groupe.

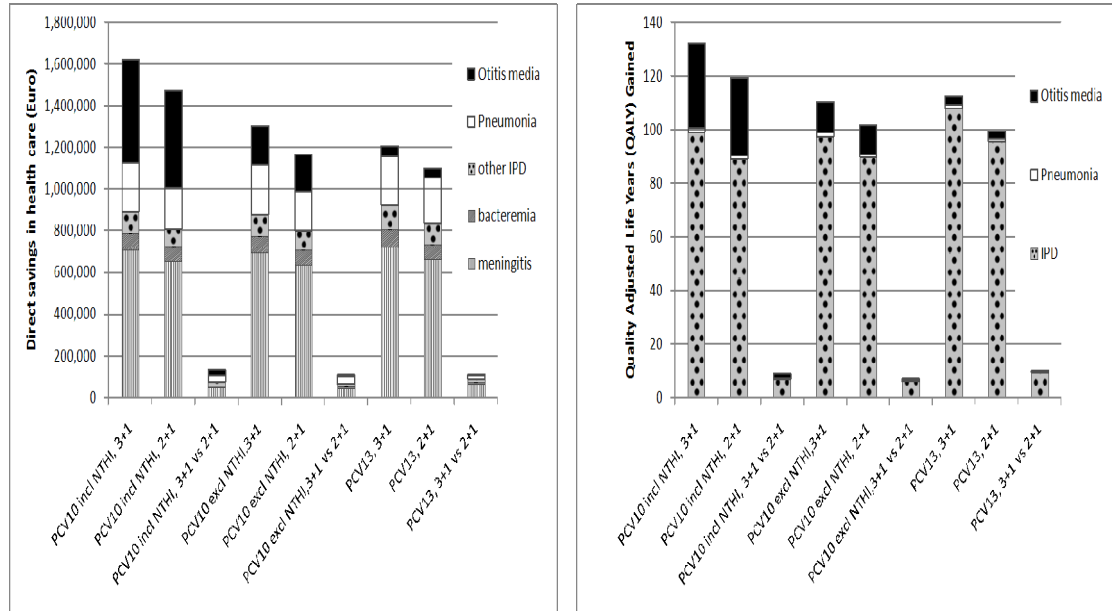
Il y a cependant lieu de se demander si la vaccination PCV7 constitue toujours une intervention coût-efficace en Belgique (et est donc toujours l'option adéquate à comparer aux vaccins PCV10 et PCV13) compte tenu du remplacement des sérotypes observé. Mais cette considération ne figurait pas au nombre des objectifs de notre étude.

Par ailleurs, les résultats ont également montré que le schéma 3+1 a très peu de chances d'être considéré comme une option valable par rapport au schéma 2+1, si le prix du vaccin par dose est constant entre ces schémas. La comparaison entre les schémas 3+1 et 2+1 n'est toutefois pertinente actuellement que pour le PCV13 qui détient une licence pour les deux schémas (alors que le PCV10 ne la possède que pour le schéma 3+1).

## Résultats – PCV10 versus PCV13

Le choix entre le PCV10 et le PCV13 était différent selon l'importance que le décideur accorde à la prévention des pathologies graves (IPD et pneumonie) dans des cas moins fréquents ou également à la prévention des pathologies bénignes (otite moyenne) chez de nombreux enfants. En moyenne, en cas de prix identiques, le PCV13 était préférable au PCV10 si l'on considère l'impact que ces vaccins ont sur les maladies graves uniquement (autrement dit, en excluant l'otite moyenne). Dans ce cas, le PCV13 permet d'éviter davantage de coûts de traitement et de gagner davantage de QALY que le PCV10 (Figure 1). Par contraste, compte tenu du nombre élevé de cas d'otite moyenne, on a estimé que le PCV10 évitait davantage de coûts de traitement que le PCV13 lorsque l'on inclut l'impact sur l'otite moyenne. En revanche, le PCV10 gagnait moins de QALY que le PCV13.

**Figure 1: Economies directes médianes (€) en terme de coûts de traitement, et QALY gagnées (médiane) selon la manifestation clinique et en fonction de différents points de vue décisionnels à propos du PCV10 (3+1) ou du PCV13 (2+1). Scénario incluant le remplacement des sérotypes, la protection croisée pour le sérotype 19A conférée par le PCV10 et excluant l'immunité de groupe.**



NTHi : non-typable *Haemophilus influenzae* (*Haemophilus influenzae* non typable), IPD: invasive pneumococcal disease (maladie à pneumocoques invasive).

Quelles que soient les options envisagées, autrement dit, en incluant ou en excluant l'immunité de groupe et l'effet du PCV10 contre l'*Haemophilus influenzae* non typable, l'impact des modulations du prix du vaccin était le plus fort et allait toujours dans le même sens : le PCV10 (3+1) serait préférable au prix public actuel en officine tandis que le PCV13 (2+1) serait préférable en cas d'égalité des prix. En utilisant le prix public actuel en pharmacie, on a constaté que le PCV10 (3+1) était plus coût-efficace que le PCV13 (2+1) dans 96% des simulations (en incluant l'efficacité contre l'otite moyenne induite par l'*Haemophilus influenzae* non typable et en excluant l'immunité de groupe), dans 88% des simulations (en excluant l'efficacité contre l'otite moyenne induite par la HiNT et en excluant l'immunité de groupe) et dans 51% des simulations (en excluant l'efficacité contre l'otite moyenne induite par la HiNT et en incluant l'immunité de groupe). En utilisant le même prix par dose pour le PCV13 que pour le PCV10, ces pourcentages étaient de 65%, 23% et 4%, ce qui fait du PCV13 l'option la plus souhaitable par rapport au PCV10 (Tableau 1).

**Tableau 1: Probabilité selon laquelle le PCV10 (3+1) est dominant ou a un rapport coût-efficacité < €30 000 par QALY par rapport au PCV13 (2+1) dans diverses hypothèses relatives au prix du vaccin, à l'immunité de groupe et à l'efficacité contre l'otite moyenne induite par *Haemophilus influenzae* non typable (HiNT). Dans chaque scénario, on part de l'hypothèse d'une protection croisée pour le sérotype 19A induite par le PCV10 et d'un remplacement massif des sérotypes.**

		PRIX PUBLIC ACTUEL EN PHARMACIE		EGALITE DES PRIX	
		Efficacité contre l'otite moyenne induite par le HiNT			
		Oui	Non	Oui	Non
Immunité de groupe pour les IPD	Oui	-	51%	28%	4%
	Non	96%	88%	65%	23%

Les résultats présentait également une sensibilité accrue aux hypothèses de remplacement des sérotypes. Si l'on part du postulat selon lequel il n'y aurait pas de tout de remplacement des sérotypes ni aucun impact additionnel du PCV10 sur l'OMA par rapport au PCV13 mais bien une protection croisée du PCV10 contre le sérotype 19A, la vaccination avec le vaccin PCV13 était préférable.

Dans le scénario où il existe un impact supérieur sur l'OMA du PCV10 versus le PCV13, où il n'y a pas d'immunité de groupe (ce qui a été observé en Belgique et dans d'autres pays européens avec le PCV7, contrairement aux USA) et où l'on inclut une protection croisée pour le sérotype 19A conférée par le PCV10, la vaccination avec le PCV13 était préférable si l'on escompte que le remplacement des sérotypes resterait bas. Si l'on exclut la protection croisée présumée pour le sérotype 19A conférée par le PCV10, la vaccination avec le PCV13 restait préférable pour des effets plus importants du remplacement des sérotypes.

Avec une hausse du remplacement des sérotypes dans les IPD (uniquement), l'avantage du PCV13 sur le PCV10 diminue, particulièrement lorsque le PCV10 induit une efficacité additionnelle contre l'OMA. Si le PCV10 produit une efficacité contre l'OMA supérieure de 10%, l'avantage va au PCV10. Cette conclusion inattendue découle de la méthode utilisée pour la simulation du remplacement des sérotypes dans notre modèle. Cependant, si l'on exclut la protection croisée présumée pour le sérotype 19A conférée par le PCV10, les résultats redeviennent clairement plus favorables pour le PCV13.

## DISCUSSION ET CONCLUSIONS

Nous avons développé un modèle de simulation de population afin d'estimer l'efficacité réelle ainsi que le rapport coût-efficacité incrémentiel du remplacement du PCV7 par le PCV10 ou le PCV13 en Belgique.

Sur la base des résultats relatifs à l'efficacité vaccinale réelle et à la charge clinique des maladies à pneumocoques, les deux nouveaux vaccins présentent un avantage clinique par rapport à la vaccination PCV7 actuelle. Un avantage qui est encore plus pertinent compte tenu de l'augmentation récente des sérotypes supplémentaires inclus dans le PCV10 et le PCV13, qui explique que le PCV7 n'a pas pleinement concrétisé les attentes de la précédente analyse du rapport coût-efficacité.

En revanche, ce qui est moins clair consiste à déterminer lequel de ces deux vaccins devrait être choisi parce que les différences entre les deux ne sont pas patentées et que de nombreuses incertitudes prévalent.

De toute évidence, le prix auquel seront offertes les deux formulations vaccinales en grandes quantités sera largement déterminant dans le choix entre les deux. Au prix de vente actuel en pharmacie, le PCV13 (2+1) est moins susceptible d'être coût-efficace que le PCV10 (3+1) (si l'on suppose une protection croisée pour le sérotype 19A). Néanmoins, après une procédure d'appel d'offres, les différentiels de prix entre les deux vaccins pourraient changer et le PCV13 pourrait devenir plus coût-efficace que le PCV10, selon les scénarios retenus.

De surcroît, l'importance relative accordée à la prévention des pathologies bénignes chez de nombreux enfants (c.à.d. l'OMA) par rapport à la prévention de pathologies très graves dans des cas moins fréquents (c.à.d. les IPD) conditionne également le choix entre ces deux vaccins.

En outre, le choix entre les deux vaccins présente une sensibilité importante aux hypothèses de remplacement des sérotypes et à la protection présumée du vaccin PCV10 contre l'OMA HiNT et contre le 19A, ce qui doit encore être démontré. En supposant que la protection du PCV10 contre les OMA est supérieure à celle du PCV13, la vaccination avec le vaccin PCV13 était préférable pour autant que l'effet du remplacement des sérotypes reste faible. Avec une augmentation de l'effet du remplacement des sérotypes et de la protection du PCV10 contre les OMA induites par la HiNT, l'intérêt de la vaccination avec le PCV13 diminue au profit de la vaccination avec le PCV10. En excluant la protection croisée présumée du PCV10 pour le sérotype 19A, les résultats étaient à nouveau favorables au PCV13.

Bien que nous ayons tenté de simuler l'évolution du *Streptococcus pneumoniae* de la manière la plus précise possible, tout en tenant compte de l'état actuel des connaissances, notre modèle est encore entaché d'importantes limitations. D'abord, nous ne modélisons pas les conséquences du remplacement des sérotypes sur chaque sérotype individuel ni les variations de pathogénicité entre les sérotypes. Ensuite, nous ne tenons pas compte de la résistance aux antibiotiques (un problème pour lequel le sérotype 19A constitue une cause de préoccupation). De plus, notre modèle n'inclut pas l'augmentation actuelle du sérotype 19A et la méthode utilisée pour simuler le remplacement des sérotypes pénalise un vaccin plus que l'autre. Enfin, nous n'avons pas modélisé les dynamiques de transmission des sérotypes pneumococciques.

En conclusion, les résultats de notre analyse ont montré de façon constante que le remplacement du vaccin PCV7 actuel par les nouveaux vaccins PCV10 ou PCV13 est opportun. Les résultats ont aussi démontré que, pour les deux vaccins, la vaccination suivant un schéma 2+1 est plus pertinente qu'un schéma 3+1. Il est toutefois ardu de déterminer lequel de ces deux nouveaux vaccins doit recueillir la préférence. L'analyse et l'interprétation des résultats du rapport coût-efficacité de notre modélisation sont rendues difficiles par la nature incertaine des futurs effets du remplacement des sérotypes et de l'immunité de groupe, de même que de la supposée protection du vaccin PCV10 contre le sérotype 19A et de son effet sur l'OMA induite par le HiNT. En effet, la modification de ces paramètres dans des limites raisonnables engendre alternativement la préférence pour le vaccin PCV10 par rapport au PCV13, ou le contraire. Les paramètres ayant le plus grand impact sur les résultats ont été identifiés comme étant l'effet du remplacement des sérotypes et la protection supplémentaire potentielle du PCV10 contre l'OMA et le sérotype 19A. Clairement le choix entre les vaccins PCV10 et PCV13 dépendra de la préférence du décideur d'opter pour la prévention seule de pathologies graves IPD dans des cas moins fréquents ou également pour la prévention de pathologies bénignes OMA chez un plus grand nombre. Le prix auquel seront offerts les deux vaccins sera aussi largement déterminant dans le choix entre les deux, ce qui souligne l'importance de la procédure d'appel d'offre visant à obtenir des prix plus intéressants.

## RECOMMANDATIONS<sup>a</sup>

- Face à la hausse observée des IPD provoquées par des sérotypes qui ne sont pas inclus dans le vaccin PCV7 actuel, il est justifié pour des raisons cliniques de passer aux nouveaux vaccins PCV (PCV10 ou PCV13).
- Il est recommandé de passer à un schéma 2+1 lorsqu'il est disponible; ce schéma est plus coût-efficace qu'un schéma 3+1. A l'heure actuelle, seul le PCV13 possède déjà une licence pour les deux schémas, tandis que le PCV10 ne la détient encore que pour le 3+1.
- Le choix entre le PCV10 et le PCV13 n'est pas clair parce que les différences entre les deux vaccins ne sont pas manifestes et impliquent de multiples incertitudes. Ce choix pourrait être influencé par les éléments suivants :
  - Le point de vue du décideur. Si ce dernier a pour objectif de prévenir surtout des cas de pathologies graves, le PCV13 constitue l'option la plus souhaitable. Si le but consiste également à prévenir des cas de pathologies plus bénignes (dont les OMA), qui sont beaucoup plus nombreuses, le PCV10 semble préférable, mais avec un degré d'incertitude important.
  - Les hypothèses retenues. L'effet du remplacement des sérotypes, et les hypothèses d'efficacité du PCV10 contre le sérotype 19A et contre l'OMA induite par l'*Haemophilus influenzae* non typable sont les paramètres qui influent le plus sur les résultats de l'analyse du rapport coût-efficacité. La modification de ces paramètres dans des limites raisonnables engendre alternativement la préférence pour le vaccin PCV10 par rapport au PCV13, ou le contraire.
  - Le prix des vaccins. Aux prix actuels en pharmacie, le PCV10 (3+1) est davantage susceptible d'être plus coût-efficace. A égalité de prix entre les deux vaccins, c'est le PCV13 (2+1) qui est davantage susceptible d'être plus coût-efficace. Il est recommandé de procéder à une procédure d'appel d'offres visant à faire baisser le prix des nouveaux vaccins; celui-ci pourrait alors être l'élément déterminant dans le processus décisionnel.

## AGENDA POUR LA RECHERCHE

- Les mécanismes de l'immunité de groupe et du remplacement des sérotypes restent peu clairs et imprévisibles. Nos recommandations risquent d'être obsolètes si ces mécanismes connaissent une évolution inattendue à l'avenir. Il y a lieu de suivre l'évolution de ces paramètres pour réévaluer la validité de nos analyses.
- L'efficacité du PCV10 contre l'OMA induite par l'*Haemophilus influenzae* non typable et la protection croisée pour le sérotype 19A restent à établir.
- Il est indispensable d'améliorer encore les modèles de simulation pour le *Streptococcus pneumoniae* en y incluant les conséquences du remplacement des sérotypes sur chaque sérotype à titre individuel, en tenant compte de la résistance aux antibiotiques et en modélisant directement les dynamiques de transmission des sérotypes pneumococciques.

<sup>a</sup> Le KCE est le seul responsable des recommandations fournies aux pouvoirs publics.



## Scientific summary

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## GLOSSARY

ABBREVIATION	DEFINITION
ALOS	Average length of stay
AOM	Acute otitis media
CAAP	Community-acquired alveolar pneumonia
CAP	Community-acquired pneumonia
CFR	Case fatality ratio
CM	Christian Mutualities
CPI	Consumer Price Index
DALY	Disability-adjusted life-year
DTP	Diphtheria Tetanus Pertussis
EMA	European Medicine Agency
GDP	Gross domestic product
GP	General practitioner
HBV	Hepatitis B vaccine
Hib	<i>Haemophilus influenzae</i> type b
IPD	Invasive pneumococcal disease
IPH	Scientific Institute of Public Health (Institut Scientifique de Santé Publique – Wetenschappelijk Instituut of Volksgezondheid)
IPV	Inactivated polio vaccine
MMR	Measles mumps rubella
MMRV	Measles mumps rubella varicella
MVTI	Myringotomy with ventilation tube insertion
NIS	National Institute for Statistics
NTHI	Non typable <i>haemophilus influenza</i>
OM	Otitis media
OPA	Opsonophagocytic activity
OPV	Oral polio vaccine
PCV	Pneumococcal conjugate vaccine
QALY	Quality-adjusted life-year
RCM-MKG	Résumé Clinique Minimum – Minimale Klinische Gegevens
RCT	Randomized controlled trial
STR	Serotype replacement
V	Varicella
VT	Vaccine serotypes

## I BACKGROUND

*Streptococcus pneumoniae* (or “pneumococcus”) is a bacterial pathogen that affects children and adults worldwide. It consists of more than 90 serotypes, which may have varying clinical consequences, depending on the serotype. It is a major cause of illness in children, especially those under the age of 2 years. *S. pneumoniae* can cause a wide spectrum of diseases. On the one hand, invasive diseases (IPD, defined as the isolation of pneumococcus in a normally sterile fluid) include meningitis, bacteraemia (presenting with or without focus of infection), bacteraemic pneumonia, sepsis, arthritis and peritonitis. On the other hand, non-invasive diseases mainly comprise lower respiratory tract infections (including non-bacteraemic pneumonia) and upper respiratory tract infections (including otitis media and sinusitis). In children, *S. pneumoniae* is one of the leading causes of meningitis, pneumonia and otitis media. Mortality and morbidity remain high despite appropriate access to care and antibiotic treatment. In various areas of the world, treatment of pneumococcal diseases is aggravated by the emergence of pneumococcal strains resistant to penicillin and other antibiotics.<sup>1,2</sup>

### I.1 THE SEVEN-VALENT CONJUGATE PNEUMOCOCCAL VACCINE

A first pneumococcal conjugate vaccine (PCV) has been introduced in the US in 2000 and contains capsular polysaccharide antigens of seven serotypes (4, 6B, 9V, 14, 18C, 19F and 23F), each of them conjugated to a carrier protein. These 7 types were responsible for 80-90% of IPD in children less than 5 years of age in the USA, 50-60% in Europe, Latin America and Africa and 30-40% in Asia.<sup>3</sup>

The seven-valent pneumococcal conjugate vaccine (denoted as “PCV7” henceforth) was licensed in 2001 in Europe but became available in Belgium only in October 2004 due to vaccine shortage. Initial vaccination uptake was low and directed exclusively at groups at higher risk for complications, as it was initially not funded for the other groups. From 2005 on PCV7 vaccination uptake increased based on individual vaccine purchase and initiatives from private health insurers in Belgium to co-pay PCV7 for children.

A previous KCE report by Beutels et al (June 2006)<sup>4</sup> examined the pre-vaccination disease burden and the potential effectiveness and cost-effectiveness of childhood vaccination using “Prevenar ®” the then licensed PCV7 vaccine. This KCE report concluded that the cost-effectiveness of universal childhood PCV7 vaccination is uncertain due to the uncertainties arising out of herd immunity effects and serotype replacement.<sup>4</sup> These indirect effects were quantified based on the then most recent (unpublished) observations from the US.<sup>5,6</sup> It argued, however, that the uncertainty, in terms of cost-effectiveness, would be lower using a 2+1 schedule, than the 3+1 schedule, which was recommended at the time by the Superior Health Council. It showed that the incremental cost-effectiveness of using the 3+1 versus the 2+1 schedule was likely unfavourable.

In June 2006, the Interministerial conference decided to introduce universal childhood PCV7 vaccination in Belgium, using a 2+1 schedule. This decision led to the inclusion of this option in the regional vaccination programmes from January 2007, with a catch up vaccination for children up to 2 years of age.

After PCV7 introduction in Belgium, the overall incidence of invasive pneumococcal disease (IPD) showed only a moderate decrease in young children, in spite of a high vaccine coverage from 2007 onwards. Data from post-licensure IPD surveillance showed a high and rapid impact on vaccine types in all paediatric age groups, but also a concomitant rise in the serotypes that are not contained in the vaccine.<sup>7</sup> The extent to which this rise is due to “serotype replacement” (i.e. replacement of vaccine serotypes by non-vaccine serotypes) is unclear, and other factors such as secular trends and antibiotic use likely play a role as well. The effectiveness (and cost-effectiveness) of PCV7 in Belgium is therefore questionable.

## I.2 TWO NEW CONJUGATE PNEUMOCOCCAL VACCINES

Two new pneumococcal conjugate vaccines (PCV) received EC authorization in 2009. These vaccines cover the 7 serotypes included in the PCV7 vaccine, as well as additional serotypes that are now responsible for a high proportion of invasive disease:

1. Synflorix or PCV10 (GSK) is a 10-valent vaccine that also contains containing antigens from the same 7 serotypes than PCV-7, together with capsular polysaccharide antigens from serotypes 1, 5 and 7F. They are conjugated for 8 of them to a surface protein D from *H. influenzae* and for 2 of them to modified Diphtheria toxin and Tetanus toxoid respectively. PCV10 received marketing authorization from the EC in March 2009, and is approved for “active immunisation against invasive disease and acute otitis media (AOM) caused by *Streptococcus pneumoniae* in children from 6 weeks up to 2 years of age”. The manufacturer claims a high protective effect on AOM, which has been estimated at 34% in a clinical trial using a 11-valent precursor vaccine.<sup>8</sup> The study suggests that PCV10 provides protection not only against AOM due to pneumococcal serotypes but also against AOM due to non typable *Haemophilus influenzae* AOM, as the carrier protein is *H. influenzae*-derived. However, the EMA has only approved PCV10 for AOM due to pneumococcal serotypes. The indication for pneumonia has not been approved by the EMA, but a large clinical trial on pneumonia and AOM is conducted in Latin America and may result in new indications.
2. Prevenar 13 or PCV13 (Pfizer) is a 13-valent (PCV13), which contains capsular polysaccharide antigens from serotypes 1, 3, 5, 6A, 7F and 19A in addition to the 7-valent serotypes, all conjugated to the modified Diphtheria toxin.<sup>9</sup> PCV13 received marketing authorization from the EC in December 2009, and is approved for “active immunization of children aged 6 weeks to 5 years for the prevention of invasive pneumococcal disease, as well as pneumonia and otitis media”.

The clinical advantage of each vaccine is difficult to establish. PCV10 may provide a higher protection against AOM, while PCV13 offers a wider coverage of serotypes causing invasive disease (the 6 serotypes additional to PCV7 caused 65% of invasive disease in children <5 years in 2008 compared to 38% for PCV10.<sup>7</sup> In addition, the incidence of serotypes not covered by any of these vaccines also rose. The choice between these vaccines must also be made in a context of uncertainty regarding future serotype replacement, and taking into account vaccine prices.



## 2 OBJECTIVES AND RESEARCH QUESTIONS

In view of the availability of these new vaccines, the present report aims to estimate the incremental cost-effectiveness of replacing PCV7 by either PCV10 or PCV13 in Belgium. We aim to take into account the indirect effect (herd immunity) and serotype replacement effects. We report results as incremental costs, incremental effects and incremental cost-effectiveness ratios, and report these for numerous scenarios, distinguishing between the various manifestations of clinical disease (this include many explicit comparisons of each of the above type of results with and without the impact on relatively mild disease caused by otitis media (i.e. apart from many sub-presentations of the results, results are also broadly grouped as IPD and pneumonia alone versus IPD, pneumonia and AOM together).

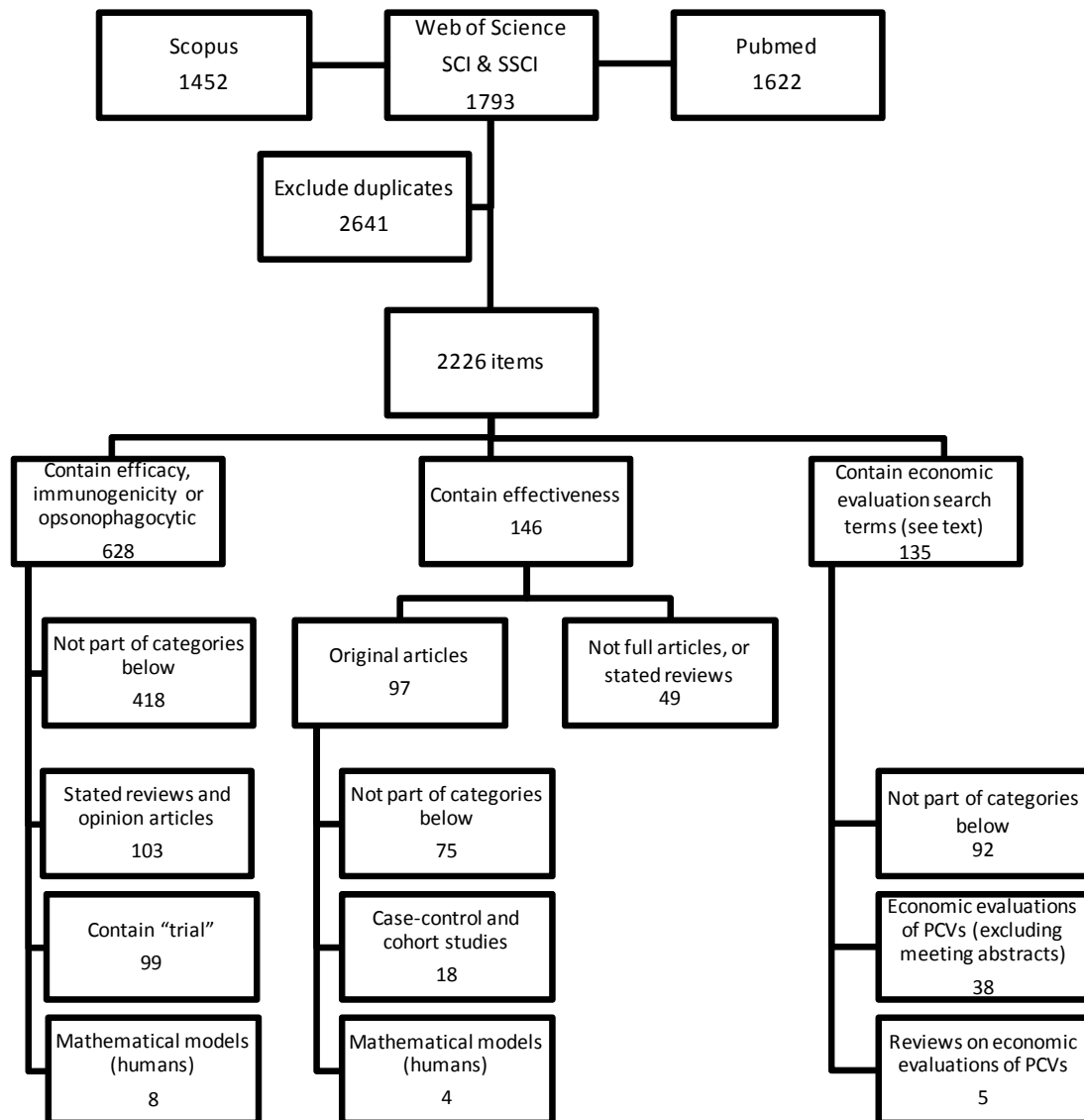
This report is organised as follows. Section 3 presents an overview of the search methods for background information from the international literature. In section 4, we present the efficacy and immunogenicity (based on data from trials) and effectiveness (based on post-PCV7 observational studies) of the various pneumococcal conjugate vaccines. In section 5, we describe the recent pneumococcal disease burden (baseline). We also review the international literature on economic evaluations and mathematical models for PCV vaccination (sections 6 and 7). Section 8 contains original research into the effectiveness and cost-effectiveness of various options of use of PCV10 and PCV13 in the Belgian childhood vaccination programme, using a tailor made simulation model.

### 3 LITERATURE SEARCHES AND METHODS

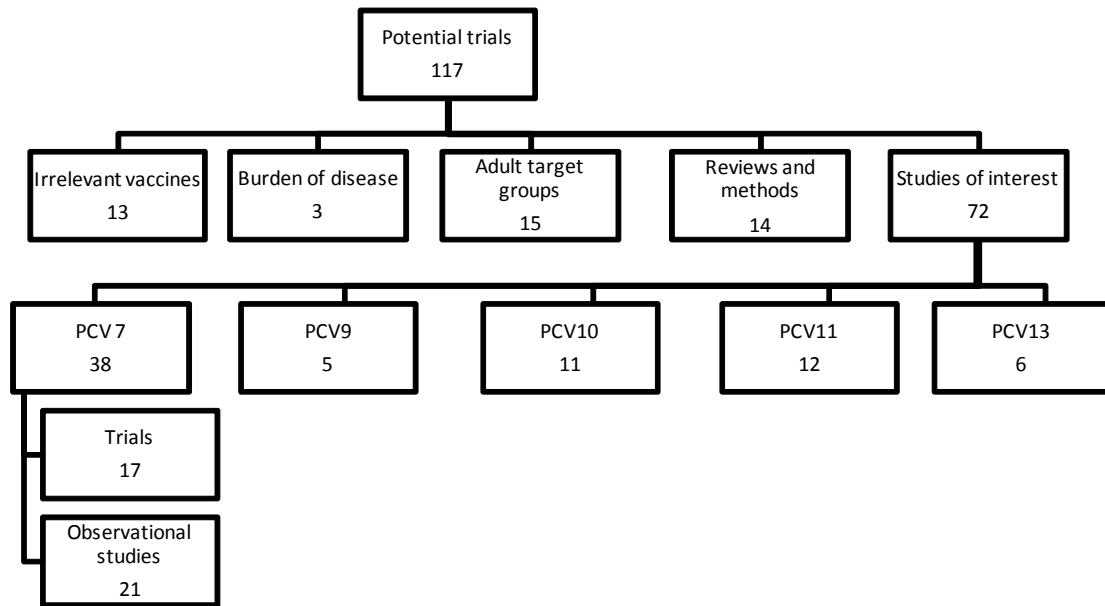
This report builds on the previous KCE report published in 2006.<sup>4</sup> In order to update the knowledge base for the current pneumococcal conjugate vaccines, a literature search was undertaken using the broad combined search string “pneumococc\* AND conjugat\* AND (vaccin\* OR immun\*)” in abstract, title or keyword fields of three databases Scopus, ISI Web of Science (SCI and SSCI) and Medline(Pubmed) to retrieve 2226 items of potential interest, which were archived since 1<sup>st</sup> January 2006 up to 1<sup>st</sup> March 2011 (Figure 1).

These items were divided using more focused search criteria to obtain full articles describing vaccine efficacy measures (using the combined search string “efficacy OR opsonophagocytic OR immunogenicity”), post-licensure effectiveness (using the single search term “effectiveness”) and economic evaluations (see further below for specific search strings). By manual inspection of title and abstract, the publications thus identified were still further refined to distinguish specific observational studies on invasive pneumococcal disease and otitis media (trials were identified before manual inspection of abstracts by using “trial” as an additional search term). As shown in Figure 2, for the studies on efficacy we distinguish different research lines pertinent to the different vaccine formulations currently licensed.

**Figure 1. Literature search results for publications of interest in Medline(Pubmed), Web of Science and Scopus (1<sup>st</sup> January 2006-1<sup>st</sup> March 2011)**



**Figure 2. Literature search results by vaccine formulation for publications potentially reporting on trials, retrieved through Medline(Pubmed), Web of Science and Scopus (1st January 2006-1st March 2011)**



## 4 IMMUNOGENICITY, EFFICACY AND EFFECTIVENESS OF CURRENT PNEUMOCOCCAL CONJUGATE VACCINES

### 4.1 SEVEN VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV7)

PCV7 (“Prevenar®”) uses a common carrier protein, cross-reactive material 197 (CRM<sub>197</sub>), a nontoxic variant of diphtheria toxin for serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. The characteristics of this vaccine as documented up to 2006 are summarized in depth in Oosterhuis-Kafeja et al.<sup>10</sup>

Key studies that were used to inform model-based calculations in the previous KCE report on PCV7<sup>4</sup> were publications of (1) the pivotal randomized controlled trial in Northern California<sup>11-13</sup>; of (2) a randomized trial in The UK comparing the full 3+1 versus a reduced 2+1 schedule<sup>14</sup> and of (3) the direct and indirect effects of the PCV7 vaccination programme in the USA.<sup>6,15</sup>

As shown in Figure 2, half of the studies on pneumococcal conjugate vaccination in children published since 2006, were on PCV7, with 34 out of 72 studies focusing on the other pneumococcal conjugate vaccine formulations.

#### 4.1.1 Clinical trials – efficacy of PCV7

We note a number of key observations from the new PCV7 trials we identified<sup>16-32</sup>:

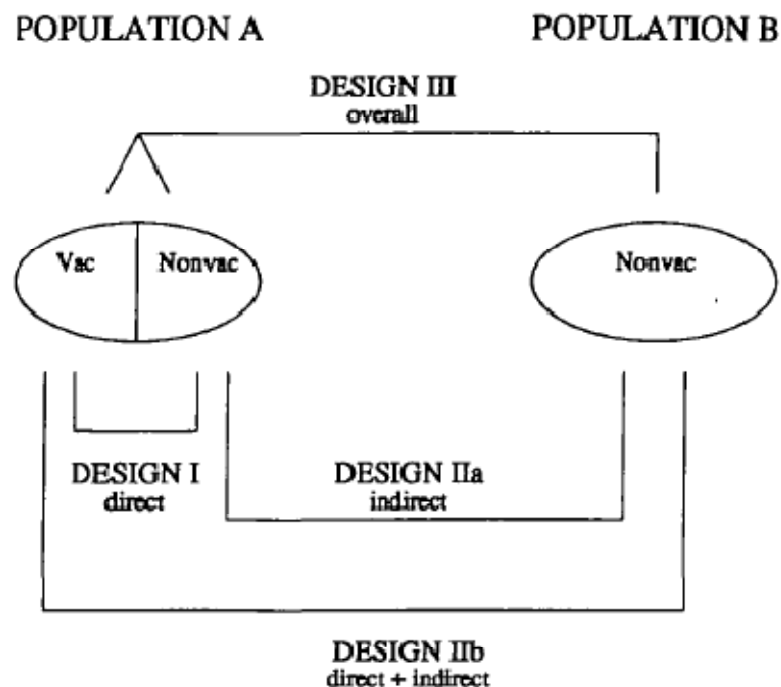
- The efficacy and safety of PCV7 is unaffected when administered concomitantly with a variety of other vaccines, such as meningococcal C conjugate vaccines, measles mumps rubella (MMR) vaccine or Diphtheria Tetanus Pertussis (DTP) vaccine combinations.<sup>16,19</sup>
- PCV7 reduces nasopharyngeal carriage of vaccine serotypes (VT), and for some serotypes there seems to be less VT carriage occurring with more doses of PCV7 administered.<sup>17</sup>
- As previously documented<sup>14</sup>, a 2+1 schedule of PCV7 (with the two priming doses at 2 and 4 months of age, as in Belgium) resulted in relatively lower immunogenicity responses to serotypes 6B and 23F, compared to a 3+1 schedule.<sup>19</sup> After priming, immunogenicity tended to be less for 6B (32% to 83% of vaccinees  $\geq$  0.35ug/ml) than for 23F (53% to 88.5% of vaccinees  $\geq$  0.35ug/ml), a tendency which was not observed with 3 dose priming (83-97% and 85-98%, respectively). Note also that with the 3+1 schedule 6B and 23F tended to give slightly lower immunogenicity after priming compared to the other serotypes. After boosting, the antibody concentrations were more generally comparable for all 7 serotypes (but again lower tendency for 6B and 23F in head-to-head comparative trials of 2+1 versus 3+1).
- In American Indians, vaccine-type pneumococcal carriage is lower among adults and unvaccinated children under 5 years, if they live with a PCV7 vaccinated person (but no such effect is observed for children aged 5-17 years). This is one of the scarce observations of herd immunity (for any infectious disease) documented in a clinical trial. It provides an empirical observation of herd immunity effects on carriage.<sup>22</sup>
- PCV7 was found to reduce respiratory tract infections compared to placebo, also when given in a 2+1 schedule in a non-randomized open trial.<sup>28</sup> This impact is however time dependent and was in one study<sup>23</sup> observed to be greater for concomitant influenza and pneumococcal conjugate vaccination versus influenza vaccination alone, but only different from placebo during the influenza season.

#### 4.1.2 Post-licensure studies – effectiveness of PCV7

A comprehensive review of publications which reported on any sort of observable impact PCV7 may have had in any sort of geographical location, is beyond the scope of this HTA report. As outlined above we took a pragmatic approach in identifying first only such studies if they were designed as a case-control study (including indirect cohort or Broome method<sup>33</sup>) or a cohort study. In addition to this, we also identified 20 publications explicitly stating that they report on the effectiveness of PCV7 (see search terms above) in observational studies.<sup>34-53</sup> Clearly, many other published studies on effectiveness were not retrieved in this way (though many of these are also discussed below), because there is confusion around the term “effectiveness” (and efficacy and impact) in the literature.

We present here the types of vaccine effects (direct, indirect and overall, see Figure 3) and the key studies under each vaccine effect. It is important to note that the indirect and overall effects are defined within the context of a particular intervention program, thus depending on the level of uptake and vaccine allocation within the population.<sup>54</sup>

**Figure 3. Halloran diagramme on vaccine effectiveness<sup>54</sup>**



**FIGURE 2.** Types of effects of vaccination and different study designs for their evaluation based on choice of comparison populations. Populations A and B are separated in every way relevant to transmission dynamics. In population A, some but not necessarily all of the people are vaccinated. In population B, no one is vaccinated. (Adapted from Halloran and Struchiner (6)).

#### 4.1.2.1 Direct effectiveness

Direct effectiveness measures the direct protective effect of the vaccine in a person who is vaccinated. It compares risks or rates in vaccinated persons and in unvaccinated persons in a population where a fraction is vaccinated.<sup>54</sup>

##### **Invasive pneumococcal diseases**

In the previous KCE report on PCV7, we were fortunate to use pre-publication information on direct effectiveness against IPD from the matched case-control study by Whitney et al.<sup>15</sup> It is noteworthy that Whitney et al.<sup>15</sup> found no significant cross protective effect of PCV7 on 19A, but did find a significant effect on 6A. Note though that serotypes 6C and 6D still had to be identified at the time the study was made.

A similar, though much smaller, study has recently been published for Canada.<sup>55</sup> Table I shows that the results in both studies are in agreement, but that for some specific estimates of direct effectiveness the Canadian study lacked sample size for statistical meaningful interpretation (i.e. regarding a single dose under age 7 months, and specific effectiveness against IPD caused by serotypes 4 and 9V). Barricarte et al.<sup>35</sup> reported similar global findings for Navarra (Spain) but with larger confidence intervals due to smaller numbers (overall effectiveness against IPD caused by vaccine serotypes in children under 5 years of age was 88% (95% CI 9-98%)). In Germany, Ruckinger et al.<sup>49</sup>, used the Broome (case control) method to estimate the direct effectiveness against IPD of one, two and three doses in the first 7 months of life to be 78.1% (3.4-96.1), 89.8% (20.6-100.0) and 94.6% (69.7-99.5), respectively. A US study using the Broome method in Massachusetts state found lower effectiveness values than in Whitney et al.<sup>15</sup>, at the same period, but had wider confidence intervals: adjusted effectiveness was 90.5% (17.7-98.9) for the full 3+1 schedule and 76.6% (50.4-88.9) for 3 doses <7 months of age.<sup>56</sup>

**Table I. Comparison of case-control studies in Quebec and the US: % effectiveness of PCV7 against invasive pneumococcal disease (95% CI)**

Schedule/serotype	Quebec; 2-59 months Deceuninck et al, 2010 <sup>55</sup>	US; 3-59 months Whitney et al, 2006 <sup>15</sup>
1 dose ≤ 7 months	32% (-228-86)	73% (43-87)
2 doses ≤ 7 months	99% (90-100)	96% (88-99)
3 doses ≤ 7 months	90% (24-100)	95% (88-98)
2+1 schedule	100% (82-100)	98% (75-100)
3+1 schedule	NA	100% (94-100)
<b>Vaccine types</b>		
serotype 4	72% (-4832-100)	93% (65-99)
serotype 6B	90% (49-98)	94% (77-98)
serotype 9V	78% (-454-100)	100% (88-100)
serotype 14	98% (84-100)	94% (81-98)
serotype 18C	92% (45-99)	97% (85-99)
serotype 19F	93% (61-99)	87% (65-95)
serotype 23F	82% (-10-98)	98% (80-100)
<b>Vaccine related types of special interest</b>		
serotype 6A	91% (-239-100)	76% (39-90)
serotype 19A	42% (-76-79)	26% (-45-62)

### ***Non-invasive pneumococcal diseases***

Very few studies tried to assess the direct effect of PCV7 on pneumonia and otitis media. O'Grady et al<sup>44</sup> found no convincing evidence that PCV7 reduced the incidence of radiologically confirmed pneumonia among subsequent cohorts of indigenous infants in the Northern Territory in Australia, although there was a non-significant trend towards an effect after receipt of the third dose at 6 months of age.<sup>44</sup>

Pelton et al<sup>45</sup> compared the difference in effectiveness between a 2+1 and a 3+1 schedule in a matched cohort study, and found a significant higher protection against inpatient treatment for lower respiratory tract infections after the primary series for the 3+1 schedule. There was no significant difference for outpatients, and the difference for inpatients disappeared after the booster dose.

#### **4.1.2.2 *Indirect effectiveness***

Indirect effectiveness refers to the population-level effect of widespread vaccination on people not receiving the vaccine.<sup>54</sup>

Studies from the US continued to show significant indirect effect among the unvaccinated groups, particularly in the elderly  $\geq 65$  years. Pilishvili documented substantial declines in vaccine types in children too young to be immunized and in adults in 2007 compared to pre-PCV7.<sup>57</sup> Though non-vaccine types also increased in all adults, in particular serotype 19A, the net effect on overall IPD was positive in all age groups  $>5$  years, with reduction in IPD incidence ranging from -18% to -43%.

In Europe, indirect effect was also observed but did not result in an overall decline everywhere, because the indirect effect on vaccine type disease was systematically accompanied by a rise of non-vaccine type incidence.<sup>58-60</sup> While the net effect on overall IPD in adults was positive in Norway in 2008 (-15% to -51% depending on age group),<sup>60</sup> it was negative in French adults where IPD incidence significantly increased in all age groups in 2008 compared to pre-vaccine.<sup>58</sup> In the Netherlands and in Navarra (Spain), no substantial changes were measured in older non-immunized children and adults.<sup>37 59</sup>

#### **4.1.2.3 *Overall effectiveness***

Overall effectiveness refers to the overall effect of a vaccination programme on a population, including direct and indirect effects. In most studies, it is measured by comparing the rates in a vaccinated population to those from the same population pre-intervention (pre and post design).<sup>54</sup>

A large number of "pre and post" studies has been published in many countries around the world, detailing the changing incidence and distribution of the types contributing to disease under the pressure of PCV7 vaccination. These studies confirm that PCV7 is very effective in reducing disease caused by the seven vaccine types, but nearly all studies signal that increasing disease trends caused by non-vaccine types replace vaccine type disease. Extensive international review studies of PCV7 vaccination programmes and their impact is provided by McIntosh & Reinert<sup>61</sup> and Rozenbaum et al.<sup>62</sup> Although they present the only comprehensive overview of such impact studies to date, it is noteworthy that McIntosh & Reinert<sup>61</sup> wrote their overview while being employees of Pfizer, the developer and producer of PCV7, PCV9 and PCV13. Rozenbaum et al received funding from both Pfizer and GSK (the developer and producer of PCV10 and PCV11) to write their review.

### ***Invasive pneumococcal diseases***

In most countries that have used PCV7 as part of a universal childhood programme, the net effect of vaccination on invasive pneumococcal disease remained positive. That is, the reduction of disease caused by the seven vaccine types and other vaccine related types (i.e. often defined as non-vaccine types of vaccine serogroups, that is 6A, 6C, 6D, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C, 23A, and 23B) was larger than the associated increase in disease caused by non-vaccine types.<sup>61-69</sup> The net reduction in IPD is manifested the most in children younger than 2 years of age. We highlight here some specific countries experiences



## THE UNITED STATES

In the United States, the use of PCV7 is associated with a large decline in IPD in general between 1998 and 2008 (76% decline in children <5 years; 45% decline over all age groups). More specifically IPD caused by vaccine serotypes (-99.5%) is virtually eliminated in children <5 years of age.<sup>70</sup> Significant indirect reductions (through herd immunity) in overall IPD in all age groups >5 years were observed, particularly in the elderly >65 years. Since 2002 a gradual increase (+29%) in the incidence of non vaccine type IPD has been observed, mainly due to 19A (+253%). Vaccine-related serotype 19A has become the most common cause of IPD in the US, responsible for almost half of IPD episodes in children <5 years of age. The main identified non-vaccine serotypes in IPD include 7F, 22F, 33F and 3.<sup>70</sup> A cause for concern is the emergence of multidrug resistant strains of non-vaccine serotypes 19A. Another concern is the emergence of serotypes 1 and 3, which are often found in pneumonia cases with empyema.

## CANADA

In Canada, the experience with PCV7 is very similar to the US, with near elimination of vaccine types in IPD, a significant decline in overall IPD despite the gradual emergence of types 19A, 3, 22F, 7F, 5 and 15C (in descending order of importance).<sup>71</sup>

Of special interest is the Canadian province of Quebec, which was the first region to intentionally introduce universal PCV7 vaccination according to a 2+1 schedule (in December 2004, whereas previously in the US unintentionally a 2+1 schedule was used due to intermittent vaccine shortages between 2000 and 2004). The impact of the vaccination programme there was lower than in the US experience (50% reduction in IPD in children <5 years of age in 2007-2008 compared to pre-universal vaccination years vs. a 76% reduction in the US). Serotype replacement occurred mainly through serotype 19A (around half of cases).<sup>55</sup>

## EUROPE

In Europe, PCV7 has been introduced in the universal infant schedule of more than 15 countries usually at vaccine uptake of about 90%, with most introductions taking place in 2006-2007.<sup>61</sup> There has been a mix of schedules (see Table 2 for examples and McIntosh et al<sup>61</sup> for a complete overview). Due to the variety of IPD surveillance systems, comparisons should be made with caution.

**Table 2. Basic characteristics of universal PCV7 programmes in a selection of European countries and Quebec**

Country	Start	Schedule (months)	Incidence of IPD caused by non vaccine types
Quebec	Dec 2004	2, 4 + 12	Relatively stable
England & Wales	Sept 2006	2, 4 + 13	Large increase
Netherlands	June 2006	2, 3, 4 + 11	Moderate increase
France	June 2006 <sup>a</sup>	2, 3, 4 + 11 2, 4 + 12 (after 2008)	Large increase
Norway	July 2006	3, 5 + 12	Stable till 2008 Mild increase in 2009
Belgium	Jan 2007	2, 4 + 12	Large increase
Denmark	Jan 2007	3, 5 + 12	Mild increase (7F)
Germany	Jan 2007	2, 3, 4 + 11-14	Relatively stable till 2007-08 Mild increase in 2008-09

a Recommended and reimbursed in 2003 for a large proportion of French infants through definition of their medical and living conditions as presenting higher risk for pneumococcal disease. IPD: invasive pneumococcal disease.

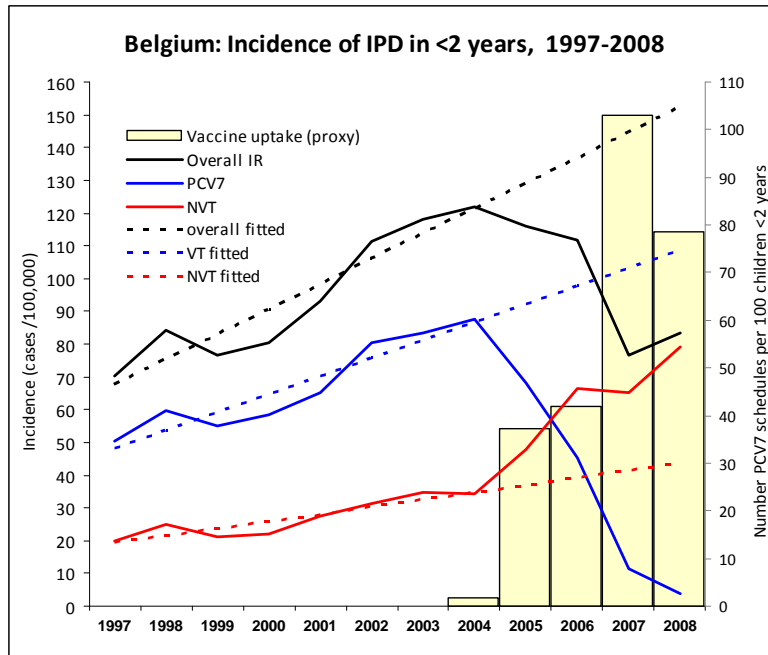
While the impact of PCV7 on vaccine type IPD is similar (a decline of around 90 to 95%), the impact on the overall incidence of IPD is clearly lower in Europe (including Belgium) than in the US, irrespective of the schedule that was used. A striking difference is the rapid increase in IPD due to non-vaccine serotypes in Europe, which has a negative influence on PCV7 impact. As a result, most European countries report a lower overall effect on all IPD compared to the US experience. In France, the net decline of IPD (assuming constant incidence) in children under 2 years of age was estimated at 21% in 2006 (95% CI: 10–31%) and 32.5% in 2007–08<sup>58 72</sup>, in The Netherlands at 44% (95% CI: 7–66%), in Norway at 52% (95% CI: 31–66%), and in Denmark at 57% (95% CI: 38–71%).<sup>38 59 73 74</sup> In most European countries (including Belgium), there is a rising IPD incidence due to non vaccine types 1, 7F and 19A, but a multitude of other serotypes are also gaining importance in many of these countries. There is emerging dominance of types 1, 5, 7F and 19A in Spain; 1, 7F and 19A in France; 19A in Portugal; 1, 3, 6A, 7F and 19A in Italy; 1, 7F, 19A, 33F and 23F in England and Wales; serotype 7F and other serotypes not present in PCV13 in Denmark; and 7F and 19A in Greece.<sup>38 58 61 75</sup> In Norway and Germany, more recent rises in non-vaccine types also involved 7F and 19A.<sup>76 77</sup> Vaccine serotypes are still prevalent in residual IPD in some countries (e.g., in Germany, serotypes 6B, 14 and 23F prevail, along with non vaccine types 1, 3, 6A and 7F).<sup>61</sup> The non-vaccine types that have replaced vaccine types in Europe are partly different from the ones in North America. Assessing the impact of these vaccines is difficult due to the fact that pre-vaccination IPD incidence was not stable. For instance, it has been suggested that serotype 1 evolved independently of vaccination in various European countries, and that serotype 19A showed a mild increase before PCV7 introduction in several countries.<sup>67</sup>

## BELGIUM

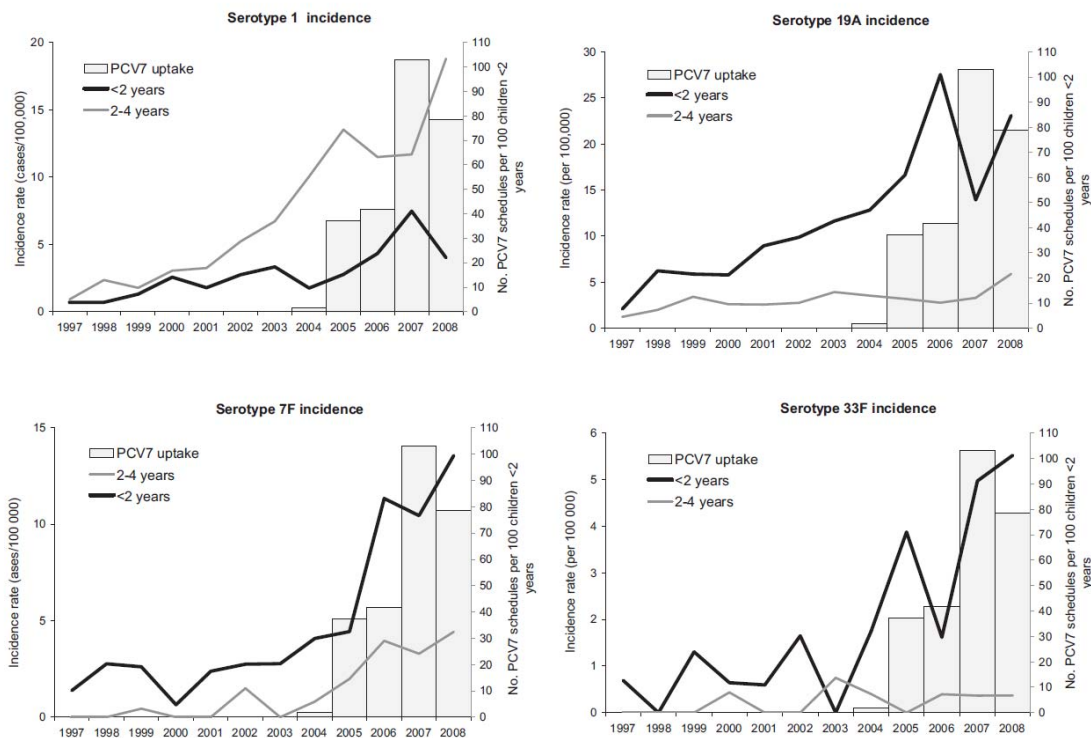
In Belgium up to 2008 there was a net IPD incidence decline of 37% in children <2 years and of 15% in children <5 years compared to pre-vaccine, after adjustment for under-reporting. However, the overall effect varied according to whether data were adjusted for other factors or not: in children <2 years it was 46% if incidences were adjusted for pre-vaccine trends and 23% if incidences were not adjusted at all (Figure 4).<sup>7</sup> In children <5 years of age, non-vaccine serotypes increased >2-fold. Compared to pre-vaccine, non-vaccine types 1, 7F, 19A, 10A, 12F, 24F and 33F significantly raised in 2008. Serotypes 1, 7F and 19A were the most prevalent and represented all together 55% of IPD in 2008. Importantly, serotypes that are not included in PCV10 and PCV13 also increased significantly (IRR = 3.18; 95% CI 1.95–5.42).

Belgian data also show that some non-vaccine serotypes, mainly 1 and 19A, started rising before the introduction of PCV7 (Figure 4 and Figure 5).<sup>7</sup>

**Figure 4. Incidence of invasive pneumococcal disease by serotype group in children <2 years of age and linear regression fitted on the 1997–2004 pre-vaccination period (dotted lines)**



**Figure 5. Incidence of invasive pneumococcal disease due to serotypes 1, 7F, 19A and 33F by age group**



There are several limitations with interpreting trends in disease incidence and comparing these between countries. Indeed, in addition to the influence of PCV7 vaccination, there are several relevant aspects to consider when interpreting these trends:<sup>73</sup>

1. Increased reporting has been observed in many countries, as a result of enhanced surveillance that followed introduction of PCV7 in a majority of countries.<sup>78</sup> This becomes a bias when studies do not adjust incidences to the under-reporting rates, as shown by comparison of adjusted and non-adjusted incidences in several EU studies.<sup>7 79 80</sup>
2. Increased detection of cases through more frequent blood culturing, especially in cases of bacteremia without focus (see for example <sup>81 82</sup>), could contribute to an increase in observed IPD incidence.
3. It is well known that secular trends occur in the pneumococcal serotype distribution. This was documented during the pre-PCV7 vaccination period over both short and long time periods in various countries.<sup>83</sup>
4. The pneumococcal serotype distribution can change quickly when different strains start circulating as part of a natural process of evolution (e.g., clones of serotype 1 have often spread rapidly, often remaining a local peculiarity, but also regularly emerging from a local community to become established in wider geographic areas).<sup>84</sup>
5. Antibiotic use differences and changes through time may influence the distribution of serotypes causing disease. For example, although in virtually all countries an increase is observed in drug-resistant clones of serotype 19A, this increase seems to have started in the pre-vaccination era in many of these countries. In Norway, which typically uses fewer antibiotics compared to other countries, the incidence of IPD caused by 19A increased significantly post PCV7, but not that of penicillin-nonsusceptible 19A.<sup>85</sup> Furthermore, several observational studies have documented a positive association between PCV7 vaccination or the number of PCV7 doses received and the likelihood of 19A isolation, including in one of the RCTs.<sup>32 86 87</sup> These facts suggest effects from both vaccination and antibiotic use on the emergence of (at least) non-vaccine serotype 19A.

Note that serotype replacement has not only been documented in relation to IPD and pneumonia, but also in relation to otitis media.<sup>88-92</sup>

Given the relatively recent insight that there exists a previously unknown serotype 6C which can replace vaccine type 6A, Millar et al<sup>42</sup> retrospectively showed that over 90% of serogroup 6 invasive pneumococcal disease and carriage strains among Navajo and White Mountain Apache communities have become 6C, a doubling compared to the pre-vaccination era. Note that, in the mean time, now also serotype 6D has been identified.<sup>93</sup> Hanage et al also showed that some cases of serotype 6C can be the results of serotype switching from the vaccine serotype 6B, representing thus escape variants emerging after PCV7 introduction.<sup>94</sup>

### ***Pneumonia and otitis media***

Jardine et al<sup>95</sup> documented reductions in hospitalisations for myringotomy with ventilation tube insertion (MVTI) after the introduction of PCV7 in Australia, of 23%, 16%, and 6% in children aged 0-1 years, 1-2 years and 2-3 years, respectively. Mackenzie et al<sup>41</sup> found no significant reduction in otitis media episodes when comparing two cohorts of indigenous infants in Australia, although there was a reduction in tympanic membrane perforation.

Ansaldi et al<sup>34</sup> reported declines in all-cause and pneumococcal pneumonia and acute otitis media hospitalisations under 2 years of age in Liguria (Italy) based on comparing ICD-coded hospitalisations three years pre-vaccination with three years post-vaccination. Surprisingly, they found no decline in hospitalizations for meningitis or sepsis, but this study had methodological limitations and population and schedule are not comparable to our settings.<sup>34</sup>

Grijalva et al estimated otitis media outpatient visit rates in the US declined by 33% (95% CI, 22%-43%) in children aged <5 years. They also found significant decreases in outpatient visit rates for acute respiratory infections in children aged <5 years.<sup>96</sup> Another US study, using time-series analysis, found a 39% (95% CI 22%-52%) reduction in all-cause pneumonia admission rates in children younger than 2 years.<sup>97</sup> Taylor et al found an overall 24% decrease in OM incidence rates based on insurance data from 9 US regions, but OM rates had already declined 19-24% prior to PCV7 introduction.<sup>98</sup>

A long term study (2001-June 2009) from France in children presenting with AOM to a network of paediatricians shows clearly that children who have AOM with fever carry significantly fewer pneumococci (-13% over the first five years), significantly fewer PCV7 serotypes of pneumococci (-61% over the first five years), and significantly more non-PCV7 groups of pneumococci (+145% over the first five years). Over the most recent years (2006-2008), both healthy children and children presenting with AOM (with different associated symptoms, including fever) progressively carried significantly more *Haemophilus Influenzae* (in 2009: 15.2% in healthy children versus 46.8% in children with AOM), and significantly fewer pneumococci (in 2009: 28.8% in healthy children versus 59.5% in children with AOM). Whereas carriage of 19A increased significantly during the pre-vaccination period, in the post-PCV7 period, there was no significant difference in serotype 19A, and serotype 6A/C carriage (personal communication, Cohen, 2011).

#### 4.1.3 Pathogenicity of serotypes

By relating IPD incidence to carriage of serotypes during 3 winter seasons (2003-2004, 2006-2007, 2008-2009) in Massachusetts (US), Yildirim et al<sup>69</sup> identified 18C, 33F, 7F, 19A, 3 and 22F as serotypes with the highest invasive capacity, and serotypes 6C, 23A, 35F, 11A, 35B, 19F, 15A and 15BC as serotypes with the lowest invasive capacity.

Using data from England & Wales (1996-2006), Trotter et al<sup>99</sup> found that serotype 1 was associated with significantly lower odds of meningitis, and serotypes 23F, 3, 6B, 19F, 18C, 6A, 22F, 12F with significantly higher odds of meningitis relative to serotype 14. Based on case:carrier ratios, they also identified - as the serotypes with the greatest capacity to cause invasive disease - serotypes 7F, 18C, 38, 9V and 14 for children aged less than 5 years, and serotypes 8, 4, 9N, 9V and 3 for everyone aged 5 years and older. These results are to be interpreted with caution since Trotter et al relate the results of local carriage studies with national data on IPD.<sup>99</sup>

Using a smaller dataset from Finland (1994-1996), Hanage et al<sup>100</sup> identified serotypes 38, 14, 18C, 19A, and 6B as having a greater risk of causing invasive disease (whereas serotype 6A, 35F and 11A had a lower odds for IPD than average).

In the pre-PCV7 period, Brueggemann et al studied the invasive potential of serotypes based on datasets from 6 countries. They identified serotypes 1, 5 and 7 as having a significantly greater odds than serotype 14 of giving rise to IPD once carried, and being 60-fold more invasive than serotypes 3, 6A and 15, those with the lowest odds.<sup>101</sup> They also found that the most invasive serotypes were the least commonly carried.<sup>101</sup> Ruckinger also found that serotype 7F was significantly associated with fatal and severe outcomes (OR>4).<sup>102</sup>

Based on these studies, serotypes 18C and 7F would be the most widely recognised as the serotypes with high invasive capacity.

Similarly Greenberg et al<sup>103</sup> estimated serotypes with the highest disease potential for paediatric community-acquired alveolar pneumonia (CAAP) to be serotypes 1, 5, 22F, 7F, 14, 9V and 19A, by decreasing rank.

In Israel in the period 2000-2004, comparing carriage in healthy children with that in children presenting with IPD and AOM, Shouval et al<sup>104</sup> found serotypes (in descending order of importance) 1, 5 and 12F to be significantly associated with IPD, and serotypes 3, 5, 1, 12F, 19A and 19F with AOM.

The above findings do not imply that these types are carried the most in patients with the specific symptoms, just that they are more likely to cause the disease state than other types, if carried. Clearly, if vaccination causes serotype replacement such that these more pathogenic types are more often carried, then there would be a disproportionate increase in the associated disease states. As far as we know, these type-specific aspects have not been considered explicitly in economic evaluation to date (see also below).

## 4.2 TEN VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10)

PCV10 contains antigens of serotypes 1, 5 and 7F in addition to the serotypes of PCV7. In PCV10, 8 serotypes are conjugated with a *Haemophilus influenzae*-derived protein D as a carrier. Serotype 18C is conjugated with tetanus anatoxin and 19F with diphtheria anatoxin.

### 4.2.1 Clinical trials – immunogenicity of PCV10

We identified 11 publications discussing trials of PCV10 since 2006.<sup>105-113</sup> After inspection of full text articles we listed in Table 3 the five amongst these, which were publications on Randomised Controlled Trials (RCTs), reporting immunogenicity measures.

**Table 3. Clinical trials used to document immunogenicity of PCV10**

Author	Countries	Design	Schedule	Number of subjects (PCV10)	Number of subjects (PCV7)
Vesikari <sup>106</sup>	Finland, France, Poland	RCT	2-3-4 + 12(18) months	1108	376
Bernal <sup>112</sup>	Philippines, Poland	RCT	6-10-14 weeks 2-4-6 months	284 285	95 96
Wysocki <sup>105</sup>	Germany, Poland, Spain	RCT	2-4-6 + 11(18) months	175 171 178	174 NA NA
			2-4 + 11(18) months	158	152
Silferdal <sup>108</sup>	Denmark, Norway, Slovakia, Sweden	RCT	3-5 + 11(12) months	175	NA
			3-4-5 + 11(12) months	176	NA
Prymula <sup>109</sup>	Czech Republic	RCT	3-4-5 + 12(15) months	226 PP vs 233 NPP	NA

RCT: randomised controlled trial; NA: not applicable; PP: prophylactic paracetamol; NPP: no prophylactic paracetamol

None of these trials evaluated the clinical efficacy of PCV10. Instead, in order to demonstrate vaccine efficacy, producers of PCV10 have focused on markers indicating an immune response was mounted (by serotype), expressed by the ELISA antibody concentrations, and opsonophagocytic activity (OPA). The latter is a lesser known marker, which provides an in vitro measurement of the ability of serum antibodies to eliminate pneumococci (i.e. it is considered to represent a direct correlate of protection against pneumococcal infection).<sup>114-116</sup> Furthermore the proportion of subjects with OPA titre >8 is believed to correlate well with pneumococcal vaccine effectiveness.<sup>115 117</sup>

For the purpose of the economic evaluation we undertake in this report, the trials in Table 3 provided basically the following information of general interest.

PCV10 induced ELISA antibody responses against all pneumococcal serotypes in the vaccine<sup>106</sup>, also when co-administered with other vaccines.<sup>112</sup>

Postvaccination antibody geometric mean concentrations tended to be lower with PCV10 than with PCV7<sup>106</sup>, but not significantly and there were some differences between schedules and settings.<sup>112</sup>

As with PCV7, after the primary course serotypes 6B and 23F induced the lowest response, relative to the other serotypes. Noninferiority of PCV10 versus PCV7 over the 3 doses primary course could be demonstrated for 8 of the 10 serotypes (not for 6B and 23F), in terms of ELISA antibody response.<sup>106</sup> It could also be demonstrated for 6B and 23F based on the proportion of subjects with OPA titre >8 using a three dose primary schedule.<sup>106</sup>

It remains somewhat unclear how reliable the OPA cut-off is to predict clinically relevant efficacy since strong post booster responses were observed for all serotypes in the reduced schedule, and experience with PCV7 seems to contradict that the 2 dose priming schedule would be significantly less efficacious with regard to clinical protection.<sup>6 108</sup>

In Wysocki et al<sup>105</sup>, who used a schedule which is in line with the Belgian schedule (2 and 4 months for the 2 dose primary course) the ELISA immune responses following 2 primary PCV10 doses were higher for 6B and vaccine related type 6A, and lower for 4, 9V and 18C compared to those following 2 doses of PCV7. They were comparable for the other serotypes. In terms of OPA titres, PCV10 induced higher responses on 6B and 19F, and comparable ones on the other PCV7 vaccine or vaccine related serotypes.<sup>105</sup> The higher response on 19F is important for the PCV10 producer to make the case that cross protection would occur for PCV10, but not (as shown in Whitney et al<sup>15</sup>) for PCV7.

Silfverdal et al<sup>108</sup> compared a 2+1 schedule (which differed from the Belgian schedule, in that the first dose was given at 3 instead of 2 months) with a 3+1 schedule. They noticed that the reduced schedule yields lower post-primary and post booster ELISA antibody levels and OPA titres.

Prymula et al<sup>109</sup> investigated the effect of prophylactic paracetamol use around the time of vaccination, and found it to significantly reduce the response on all markers of immunity, on all 10 serotypes in PCV10, and those of jointly administered vaccines. Using these and other data from the same study, Prymula et al<sup>118</sup> showed that PCV10 (like PCV7 and PCV9) reduced nasopharyngeal carriage of vaccine type pneumococci by on average 21.7% compared to PCV7. Non-vaccine types were carried relatively more with PCV10, especially pre-booster, while carriage of other pathogens was unaffected (eg, *Haemophilus Influenzae* type B).

Chevallier et al<sup>111</sup> described safety and tolerability focusing on co-administrations as reported in the different trials in Table 3. These results were more recently confirmed by Bernal et al<sup>119</sup> for different co-administrations. It appears that the following combination vaccines can be administered at the same visit with PCV10: diphtheria-tetanus-acellular pertussis vaccine (DTPa), hepatitis B vaccine (HBV), inactivated polio vaccine (IPV), *Haemophilus influenzae* type b vaccine (Hib), diphtheria-tetanus-whole cell pertussis vaccine (DTPw), measles-mumps-rubella vaccine (MMR), varicella vaccine (V), meningococcal serogroup C conjugate vaccine (CRM<sub>197</sub> and TT conjugates), oral polio vaccine (OPV) and oral rotavirus vaccine.

Although there was a tendency for more frequent fever episodes with PCV10, this was not significantly different to PCV7. Knuf et al<sup>110</sup> reported on immunogenicity of other vaccines when they are co-administered with PCV10 or PCV7, and also found no statistically significant reductions in immune response. Vesikari et al<sup>107</sup> reported on the safety and immunogenicity of booster doses in Finland (half the recruits from the above trial by Vesikari et al primed by PCV10, half had been primed by PCV7 and were newly recruited for this new study), using either PCV10 or PCV7 as a booster dose, co-administered with measles mumps rubella varicella (MMRV) vaccine or DTPa-HBV-IPV/Hib (Infanrix hexa) hexavalent vaccine. No significant impacts were found.

Focusing on serotypes 19A and 19F, Poolman et al<sup>120</sup> used trial data to confirm that vaccination with either PCV7 or PCV10 induces sufficiently high concentrations of antibodies against serotype 19F, but also to emphasize that higher levels of functional antibodies (OPA) against 19F and 19A polysaccharides were induced by PCV10 than by PCV7. They argued that the conjugation method used in PCV10 is such that it provides better cross protection to serotype 19A than PCV7.

Serotype 19A has become an important serotype of residual IPD in countries that introduced universal PCV7 vaccination (see below).

Since PCV10 is not widely used yet, it has to our knowledge not been demonstrated to which extent it would induce herd immunity, and whether the herd effects would be comparable to those induced by PCV7 for common serotypes (and given the same conjugation method, also by PCV9 and PCV13). Since PCV10 was shown to reduce nasopharyngeal carriage of vaccine type pneumococci (see above in this section), a basic prerequisite for the potential to induce herd immunity is fulfilled.

#### 4.2.2 Clinical trials – efficacy of PCV10

Of major public health interest is the ability of PCV10 to prevent clinical non-invasive disease in children. The only trials assessing the clinical efficacy of pneumococcal conjugate vaccines of higher valency than PCV10, were conducted using one of the PCV10 precursor vaccines (different formulations of PCV11) aiming to assess its efficacy against AOM.<sup>121-123</sup>

In addition to the 10 serotypes in PCV10, PCV11 contained also serotype 3 (apart from this addition there were no substantial differences in vaccine design between PCV10 and PCV11). The immunogenicity and reactogenicity of PCV11 has been described in a series of publications predating 2006<sup>124-131</sup>, which are summarised in the previous KCE report<sup>4</sup>, and Oosterhuis-Kafeja et al.<sup>10</sup>

Prymula et al<sup>8</sup> trialled PCV11 in 4968 infants, who were randomly assigned to receive either PCV11 or hepatitis A vaccine at the ages of 3, 4, 5, and 12–15 months (with follow-up until the end of the second year of life). Parents of children participating the trial were asked to consult their paediatrician if their child was sick, had ear pain, or had spontaneous ear discharge. Children with suspected AOM were then referred to ear, nose, and throat specialists, who functioned as study investigators. They confirmed the clinical diagnosis of otitis media by either the visual appearance of the tympanic membrane (ie, redness, bulging, loss of light reflex) or the presence of middle-ear effusion (by simple or pneumatic otoscopy or by microscopy). Additionally, at least two of the following symptoms were required (within 14 days preceding clinical diagnosis): ear pain, ear discharge, hearing loss, fever, lethargy, irritability, anorexia, vomiting, or diarrhoea.<sup>8</sup> Using this approach, the efficacy of PCV11 against clinically diagnosed AOM was estimated at 33.6% (95% CI 20.8-44.3%), which was in agreement with a case definition based on such episodes with fever of 38.5°C or more (33.9%; 95%CI 15.8-48.0%). As could be expected, similar or higher estimates were obtained for more specific definitions, such as AOM caused by bacteria (42.1%; 95%CI 27.7-53.7%), by pneumococcus (51.5%; 95%CI 36.8-62.9%), by *Haemophilus influenzae* (35.6%; 95%CI 3.8-57.0%), and by non-typable *Haemophilus influenzae* (35.3%; 95%CI 1.8-57.4%).<sup>8</sup> An excellent overview of the evidence regarding the efficacy of different PCV formulations in reducing AOM is provided by De Wals et al.<sup>132</sup> They modelled vaccine efficacy against all-cause AOM episodes, and found that the most influential factors for differences in vaccine efficacy observed in the different PCV trials were bacterial replacement and the *Haemophilus influenzae* protein D protection against AOM. Indeed, when they corrected for the prevalence of otopathogens in the control groups of the different trials, they estimated the vaccine efficacy of PCV11 over PCV7 at 10.3 to 11.2% (assuming no serotype replacement), which reduced to 3.1-5.2%, assuming additionally no impact on *Haemophilus influenzae*. When they assumed replacement would occur of vaccine-related otopathogens by other pathogens (to the extent as observed in a Finnish PCV7 trial), they estimated the difference in vaccine efficacy against AOM at 20-23.3%.<sup>132</sup>



The protection of PCV10 against AOM due to non-typable *Haemophilus influenzae* has also been studied in chinchillas. Immunized chinchillas showed antibody levels against the protein D carrier that were shown to prevent non-typable *Haemophilus influenzae* AOM. However, the magnitude of the impact of the protein D component remains to be documented.<sup>133</sup>

In a serotype specific analysis, Prymula et al<sup>8</sup> found no impact of PCV11 on serotype 3-associated AOM. This finding and the relatively lower immunological response measures for serotype 3, led the PCV11 developer to drop serotype 3 from the formulation, and thenceforth develop, produce and market PCV10.

Preliminary results of a large PCV10 efficacy trial (COMPAS) in Latin American countries which had no PCV7 programme, showed a reduction of 7.3% (95%CI 2.1-12.3%) against suspected community-acquired pneumonia (in-patient and outpatient), and 23.4% (95%CI 9-36%) against radiologically confirmed pneumonia according to WHO criteria.<sup>134 135</sup> Due to the observation that PCV10 yields lower response in 2+1 schedules for some serotypes, and given that significant clinical efficacy of PCV11 was shown only in 3+1 schedules, the European Medicine Agency (EMA) currently licenses PCV10 only under a 3+1 schedule.

No data on PCV10 effectiveness are available to date.

### 4.3 THIRTEEN VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV13)

The currently licensed PCV13 contains antigens of serotypes 1, 3, 5, 6A, 7F and 19A in addition to the serotypes of PCV7. All antigens are conjugated with CRM<sub>197</sub>, the same modified diphtheria anatoxin as is used in PCV7.

Building on pre-2006 publications<sup>136-142</sup>, since 2006 a precursor 9-valent vaccine (PCV9) containing antigens of serotypes 1 and 5 (additional to those in PCV7) was tested in trials in The Gambia<sup>143 144</sup> and South Africa.<sup>145</sup> Furthermore a combination meningococcal C and PCV9 vaccine was trialled in The UK<sup>146</sup> and Iceland.<sup>147</sup>

#### 4.3.1 Clinical trials – immunogenicity of PCV13

Six publications were identified of trials on PCV13.<sup>148-153</sup> As for PCV10, none of these trials assessed the clinical efficacy of PCV13. Since PCV13 was developed with the same technique as PCV7, the trials are less diverse in scope than the trials for PCV10 or PCV7.

The PCV13 trials basically demonstrated non-inferiority and safety for PCV13 compared to PCV7, for different schedules and co-administrations, though lower values were observed for 6B in a 2+1 schedule. However, the pivotal trials were conducted with a PCV13 formulation that did not contain the excipient polysorbate 80 (P80) in contrast with the marketed formulation.<sup>9</sup> A “bridging study” was then conducted to compare the immune responses elicited by PCV13 with and without P80. This study showed lower overall immune response with the P80 formulation, especially for serotypes 6B and 23F. Nevertheless, non-inferiority was met for all 13 valences after the booster injection, but was not met for valences 6B and 23F after primary vaccination.<sup>a</sup>

They also showed that there are sufficient immune responses for the additional serotypes, both in terms of ELISA immune responses and OPA, and that the efficacy and safety of co-administered vaccines is not adversely affected when given at the same visit as PCV13. However, functional immune responses were lower after the primary schedule for serotypes 1, 3 and 5. It is also noteworthy though that there are indications for some kind of an impaired immune memory response to serotype 3, but the clinical significance of this remains uncertain.

<sup>a</sup> The EMA criteria state “Non-inferiority to antibody response for each of the serotypes in the registered vaccine is desirable, but not an absolute requirement. Registration of products in which one or more serotypes do not meet non-inferiority criteria would have to be decided on an individual basis.”<sup>9</sup>

Indeed, serotype 3 exhibited the lowest IgG responses of the 6 additional serotypes after the booster dose, but it exceeded the preset acceptance level of 70%, and the functional OPA antibody levels were comparable, with 98% of subjects exhibiting OPA responses >8 (i.e. indicating that protection is likely).<sup>149 152 153</sup>

In Kieninger et al<sup>153</sup>, the proportions of OPA responders (>8) for serotype 3 were high after both the primary series (99.0%) and the booster dose (98.0%). Although OPA GMT was on average higher after the primary series than after the booster dose, this difference was non-significant at 95% confidence.

Furthermore, the immune responses to serotype 3 were compared between a "primed" (PCV13 primary series + PCV13 booster) and an "unprimed" (PCV7 primary series + PCV13 booster) group of children.<sup>153</sup> The proportions of children achieving adequate ELISA IgG and OPA responses were similarly high in the two study groups, although the IgG GMCs and OPA GMTs were (non-significantly) lower in the primed group. These observations may indicate that a hyporesponsive state to serotype 3 is not induced by PCV13.

**Table 4. Clinical trials used to document immunogenicity of PCV13**

Author	Country	Design	Schedule (months)	Number of subjects (PCV13)	Number of subjects (PCV7)
Esposito <sup>149</sup>	Italy	RCT	3, 5 + 11	303	303
Snape <sup>151</sup>	UK	RCT	2, 4 + 12	141	145
Bryant <sup>148</sup>	US	RCT	2, 4, 6	122	127
Yeh <sup>152</sup>	US	RCT	2, 4, 6 + 12(15)	334	332
Kieninger <sup>153</sup>	Germany	RCT	2,3,4 + 11(12)	302	303
Gadzinowski <sup>150</sup>	Poland	RCT	2,3,4 + 12	135 (lot 1) vs. 134 (lot 2)	NA
Study 009 <sup>9</sup>	Poland	RCT	2, 3, 4 + 12	250 13+P80 vs. 250 13-P80	NA

RCT: Randomised controlled trial; NA: not applicable

13+P80: PCV13 formulated with polysorbate 80

13-P80: PCV13 formulated without polysorbate 80

In combination with the inefficacy found for serotype 3 AOM prevention with PCV11<sup>8</sup> and the similarities between PCV11 and PCV13 in serotype-specific immunogenicity for common serotypes, the immunological observations on serotype 3 indicate that the PCV13-induced immune response is not sufficient to kill serotype 3 strains in mucosa. However, this does not imply automatically that this insufficiency would also apply to systemic infections like IPD. Currently there is no strong evidence in humans to confirm the latter potential implication. On the contrary, a recent challenge study in rhesus macaques showed good indications that PCV13 would provide protection in humans against IPD with serotypes 1, 3 and 5, even at relatively low OPA titers.<sup>154</sup>

A remaining concern with using PCV13 may be the relatively lower immune response for serotypes 6B and 23F observed with 2+1 schedules versus 3+1 schedules for both PCV7 and PCV13. Among the RCTs on PCV13 in Table 4, Snape et al<sup>151</sup> is closest related to the current Belgian schedule; however the PCV13 formulation used in this study did not contain polysorbate 80. In the model input parameter session, we propose adjustments for this observation.

No data on PCV13 effectiveness are available to date.

## 5 DISEASE BURDEN IN BELGIUM

The disease burden before the universal PCV7 vaccination in Belgium is described in the former KCE report and summarized in Table 5.<sup>4</sup> Note that the disease burden of pneumonia and AOM in Table 5 is not limited to that which is definitely related to pneumococcus.

**Table 5. Estimated annual disease burden of pneumococcal infections pre-vaccination (2005) in Belgium, all ages pre-vaccination**

Health state	Number of cases
IPD infections	1,403
Meningitis	96
Bacteremia	500
Other	807
Deaths	
Meningitis	12
other IPD	41
Multiple cause pneumonia	608
Life-years lost	
Meningitis	347
other IPD	663
Multiple cause pneumonia	6,631
Quality-Adjusted Life-Years lost	
IPD	1,122
Multiple cause pneumonia	6,869
All-cause AOM	1,182

Source: Beutels et al.<sup>4</sup>. IPD: invasive pneumococcal disease; AOM: acute otitis media

This section describes the evolution of the disease burden with *S. pneumoniae* under the influence of universal PCV7 use in Belgium. The description is mainly based on recent data obtained from Pedisurv (Belgian Institute of Public Health) and the National Reference Laboratory; from the GP sentinel network INTEGO; from the Carenet database of the Christian Mutualities and from the death certificates of the Flemish Community.

PCV7 was made part of the regional routine vaccination programmes in Belgium in January 2007, with 2 priming doses at 2 and 4 months of age, and a booster dose at 12 months. Additionally, catch-up vaccination was included for children up to 2 years of age. PCV7 vaccine uptake was estimated at more than 95%, more than 90% and 81-89% for the first, second and final dose, respectively in Wallonia and Flanders in 2008-2009.<sup>155 156</sup>

In the following subsections, we describe the evolution of the disease burden in Belgium after the introduction of PCV7, using as much as possible the most recently available data sources.

## 5.1 INVASIVE PNEUMOCOCCAL DISEASE (IPD)

In Belgium, a national population-based surveillance is conducted in children <16 year olds to monitor post-vaccination pneumococcal epidemiology. This surveillance is based on two prospective and active systems. On the laboratory side, the national reference laboratory (NRL) receives isolates from a stable number of around 100 hospital laboratories distributed all over the country (62% of all laboratories in 2008). It performs serotyping and antibiotic sensitivity testing. On the clinical side, clinical data and vaccination status are collected by a network of paediatricians (Pedisurv) coordinated by the Scientific Institute of Public Health from October 2005 onwards. Cases are matched and these two systems covered ~86% of all confirmed IPD cases in children <5 years in 2008. Data are adjusted to under-reporting over time by capture-recapture method.

Most of the generated data focused on the evolution of the incidence and serotype distribution of IPD in children. This surveillance showed that the serotype distribution of IPD changed over the years, with PCV7 serotypes disappearing and other serotypes taking their place (i.e. "serotype replacement"), thus substantially eroding the impact of PCV7 on the incidence of IPD.<sup>7</sup> There was a net reduction in IPD incidence under 2 years of age, which was less pronounced in >2 years of age. This was also documented in some other European countries (see section 4.1 above), and appears to be in line with the general observation that the use of PCV7 has been more effective in the US<sup>157</sup>, and (to a lesser extent) Canada.<sup>55</sup>

In particular, serotype 19A has shown a marked and significant rise, representing 28% of all IPD cases <2 years in 2008.<sup>7</sup> It rose mainly in the age targeted by PCV7 (<2 years) but presented a mixed picture, increasing before PCV7 use and further rising after vaccination. It should be noted that the prevalence of penicillin and erythromycin non-susceptible 19A serotypes rose, but 19A susceptible isolates also increased substantially in the same period. This suggests that antibiotic pressure may have played a role but cannot explain alone the 19A rise. This recent 19A trend is thus partly beyond understanding and is likely multi-factorial.

The last Belgian data available through Pedisurv and from the national reference laboratory date from 2009. The number of cases and the distribution of serotypes for those aged under 16 years is given in Table 6.

**Table 6. Number and distribution of serotypes causing invasive pneumococcal disease in people under 16 years of age, according to clinical diagnoses (Belgium, 2009)**

Serotype	Bacte-remia	Menin-gitis	Pneumo complic-ated	Pneumo non complic-ated	Shock	Un-known	Other	Total
<b>PCV7</b>		4	1		2	3		10
14						1		1
19F		1			2			3
23F		1				1		2
4			1					1
6B		2				1		3
<b>PCV10</b>	25	5	42	76	1	81		230
1	6	2	29	54	1	44		136
5	7		10	14		13		44
7F	12	3	3	8		24		50
<b>PCV13</b>	22	14	7	9		33	1	86
19A	17	9	7	7		26	1	67
3	3	2		2		4		11
6A	2	3				3		8
<b>Not in vaccine</b>	35	14	1	13	2	31	1	97
10A	3				1	4	1	9

Serotype	Bacte-remia	Menin-gitis	Pneumo-complic-ated	Pneumo-non com-plicated	Shock	Un-known	Other	Total
10B				1				1
11A	1	1						2
12F	5	2		3		8		18
15A		1		1		1		3
15B						1		1
15C	1							1
17F						1		1
19	1							1
22F	7				1	1		9
23	1							1
23A						1		1
23B	1			2				3
24						1		1
24B	1							1
24F	5	2		2		4		13
27						1		1
29	1	2						3
2B						1		1
31						1		1
33			1					1
33F	3	4		2		2		11
35		1				1		2
38	4					1		5
7		1		1		1		3
8	1			1				2
9N						1		1
Unknown	12	8	26	22	3		2	73
Total	94	45	77	120	8	148	4	496

Note: subtotals are additional to previous subtotals (i.e. serotypes for PCV10, are those additional to PCV7, and serotypes for PCV13 are those additional to PCV10). Source: Pedisurv / IPH.

Table 6 shows that in 2009, only 10 out of 423 IPD cases aged <16 years with known serotypes were due to serotypes covered by PCV7. An additional 230 cases were due to serotypes 1, 5 and 7F (covered by PCV10 and PCV13), and an additional 86 IPD cases were due to 19A, 3, 6A; all three covered by PCV13 (3 perhaps to a lesser extent); and two of these (6A certainly and perhaps 19A) partially by PCV10 (see also vaccine efficacy sections above). For all IPD, this would bring the theoretical coverage of PCV7, PCV10 and PCV13 in this age group to 2.4%, 56.7% (max 72.6%) and 77.1% (min 74.5%), respectively. For meningitis, the theoretical coverage of PCV10 and PCV13 would be lower and amount to 24.3% and 62.2%, respectively.

Yet, as shown in Table 7 a substantial proportion of IPD is caused by serotypes which are not covered by any of the 3 vaccine formulations. Indeed, 14 out of 37 (37.8%) meningitis cases with known serotypes, were caused by non-PCV13 serotypes. Similarly 35 out of 82 (42.7%) bacteremia cases with known serotypes were caused by non-PCV13 serotypes (see Table 6 and Table 7).

**Table 7. Distribution and invasive capacity of serotypes causing invasive pneumococcal disease in people under 16 years of age, according to clinical diagnoses (Belgium, 2009)**

			Serotypes	High invasive capacity*	Meningitis	Bacteraemia	Pneumonia	
PCV7	PCV10	PCV13	4		-	-	0.7%	
			6B		5.0%	-	-	
			9V	Y	-	-	-	
			14	Y	-	-	-	
			18C	Y	-	-	-	
			19F	Y	2.5%	-	-	
				23F		2.5%	-	-
				1	Y	5.0%	6.8%	55.7%
				5	Y	-	8.0%	16.1%
				7F	Y	7.5%	13.6%	7.4%
				3	Not in children	5.0%	3.4%	1.3%
				6A		7.5%	2.3%	-
				19A	Y (not more than 19F)	22.5%	19.3%	9.4%
NON-PCV VACCINE TYPES			33F	Y	10.0%	3.4%	1.3%	
			22F	Y	-	8.0%	-	
			38	Y	-	4.5%	-	
			24F		5.0%	5.7%	1.3%	
			12F		5.0%	5.7%	2.0%	
			29		5.0%	1.1%	-	
			10A		-	3.4%	-	
			11A		2.5%	1.1%	-	
			other		7.5%	6.8%	4.7%	
			non-PCV13		35.0%	39.8%	9.4%	
			non-PCV10		75.7%	69.5%	20.1%	
			non-PCV10 without 19A		51.4%	48.8%	10.7%	
			non-PCV13 with 3		43.2%	46.3%	10.7%	

\* High invasive capacity as identified by Trotter et al<sup>99</sup>, Yildirim et al<sup>69</sup> and Brueggemann et al<sup>101</sup>, modified by opinions of the expert committee of this report. Source: Perdisurv / IPH

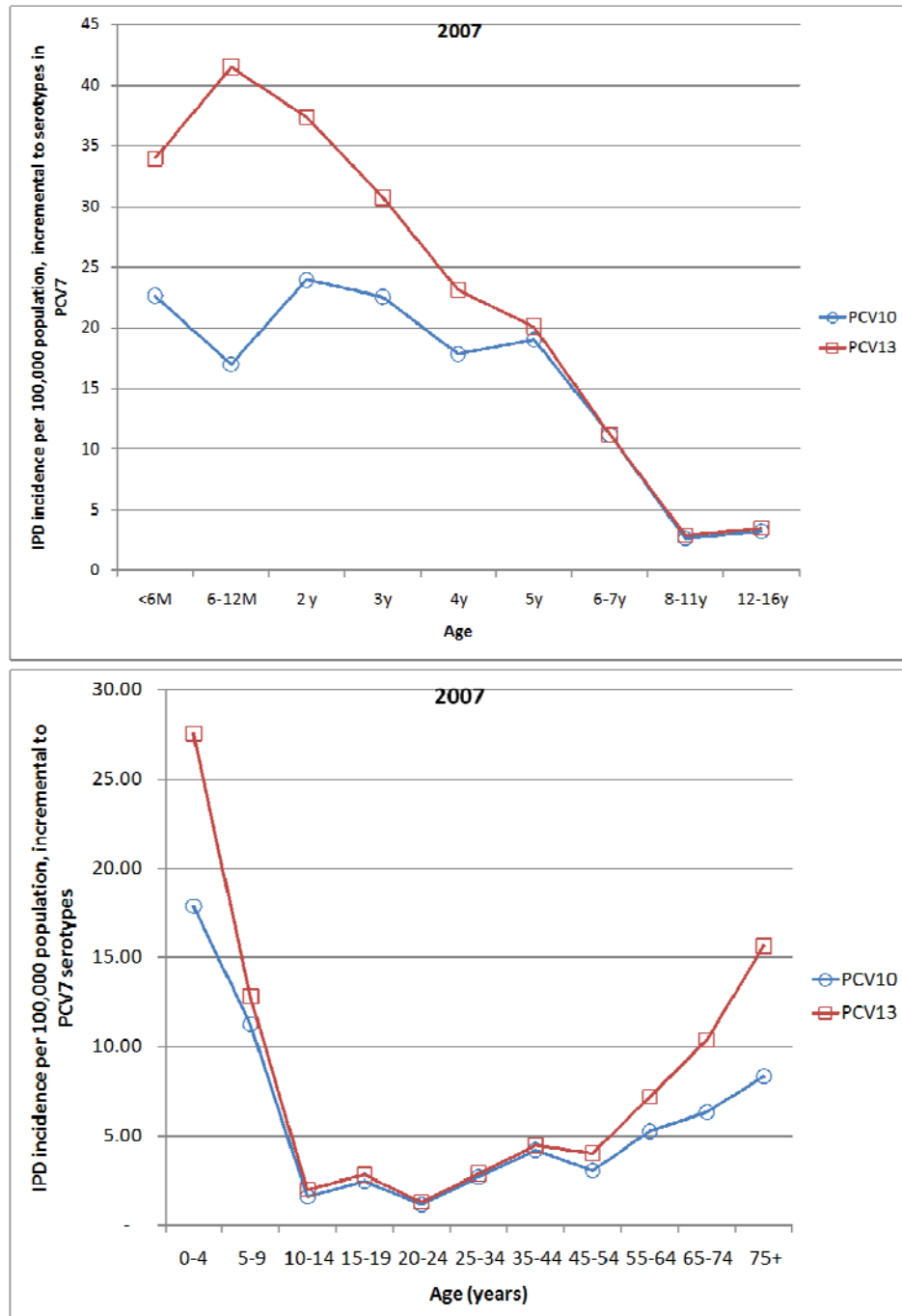
In view of the evolution of the serotype distribution observed since the introduction of PCV7 and the potential for rapid rises in IPD caused by non-vaccine pneumococcal serotypes when vaccination exerts ecological pressure on nasopharyngeal colonisation, this observation may add to the uncertainty on the effectiveness of these vaccines in reducing IPD incidence over time. Table 8 summarises the clinical diagnostic information, but distinguishes different age categories to show that the most severe IPD cases (in those aged less than 16 years) occur more often under the age of 1 year and between 1 and 2 years than at higher ages.

**Table 8. Age dependent frequency of clinical diagnoses associated with IPD cases under age 16 years (Belgium, 2009)**

IPD clinical diagnosis	Age				Unknown	Total
	<1	[1, 2[	[2, 5[	5+		
<b>Bacteremia</b>	42	25	23	4	-	94
<b>Meningitis</b>	27	5	3	10	-	45
<b>Other</b>	1	1	2	-	-	4
<b>Pneumo complicated</b>	6	9	37	25	-	77
<b>Pneumo non complicated</b>	19	16	52	33	-	120
<b>Shock</b>	4	2	-	2	-	8
<b>Unknown</b>	36	29	53	29	1	148
<b>Total</b>	135	87	170	103	1	496

Figure 6, Figure 7 and Figure 8 show the IPD incidence per 100,000 population that is minimally covered (broadly and in theory) by PCV10 and PCV13, incremental to the “residual” IPD incidence from PCV7 serotypes that occurred in 2007, 2008 and 2009, respectively. It shows that the incremental coverage of PCV10 and PCV13 increases over time. That is, IPD caused by PCV7 serotypes is replaced increasingly by IPD caused by the additional types in PCV10 and PCV13. These figures also show a similar age-specific pattern over all the years. In the group of those aged under 16 years, PCV13 additional coverage compared to PCV10 decreases with age, with the most important gains in coverage expected from PCV13 under the age of 2 years. In the group which shows all ages, the main observation is that the additional coverage offered by PCV10 and PCV13, increases again with age after age 25 years.

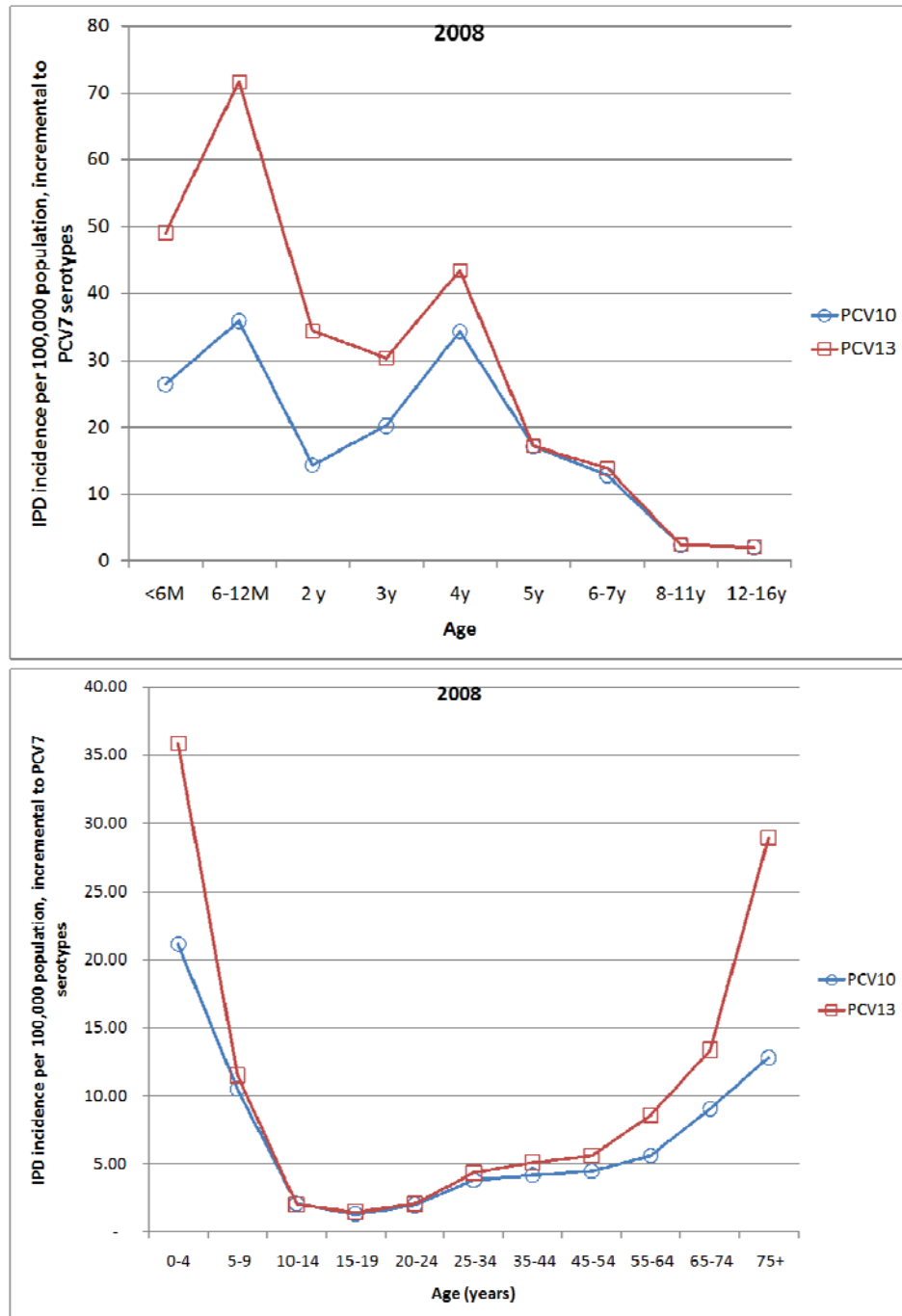
**Figure 6. IPD incidence per 100,000 population that is covered by PCV10 and PCV13, incremental to the “residual” IPD incidence from PCV7 serotypes (2007)**



Top panel: ages under 16 years; Bottom panel: all ages. Source: Reference Laboratory

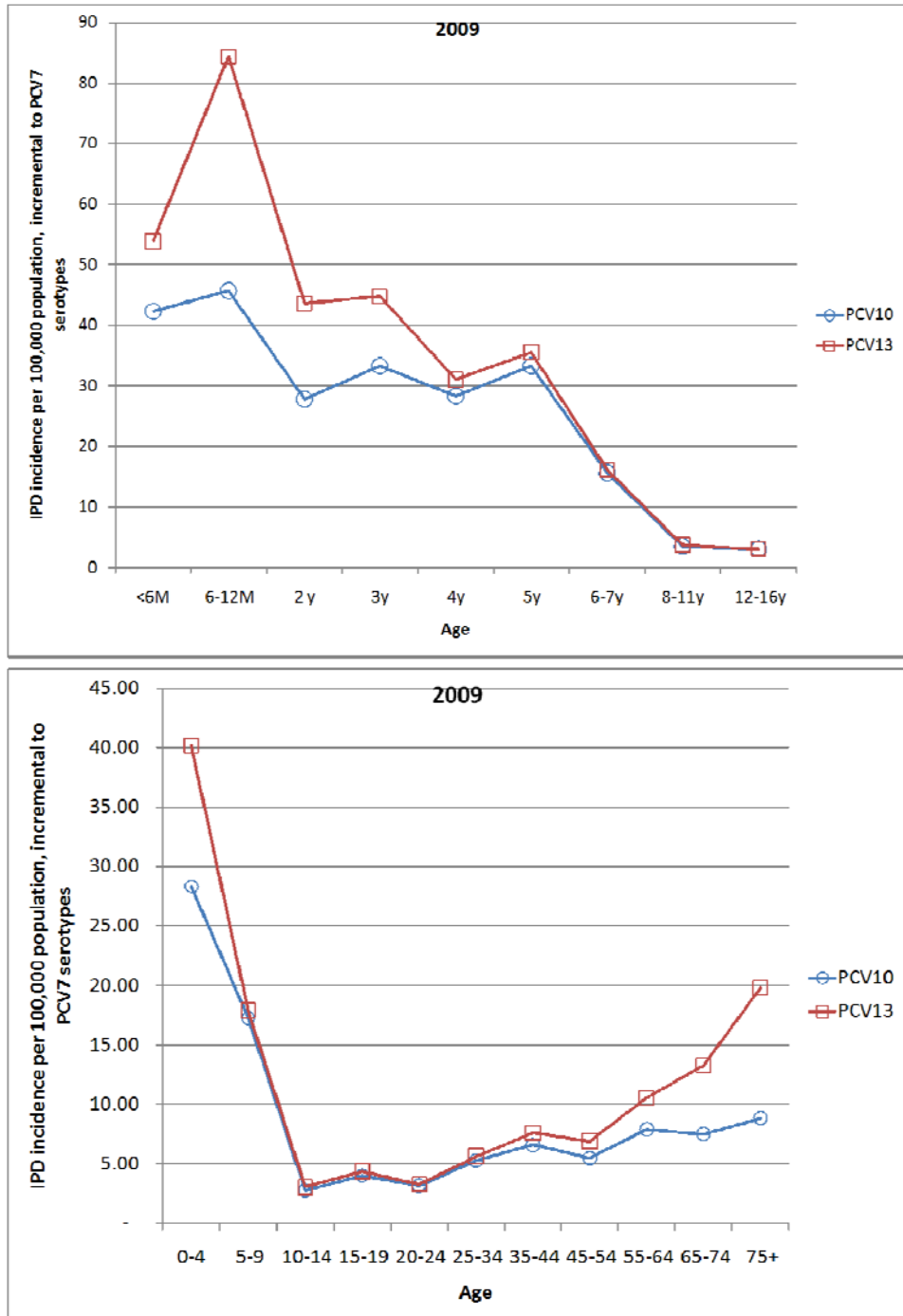


**Figure 7. IPD incidence per 100,000 population that is covered by PCV10 and PCV13, incremental to the “residual” IPD incidence from PCV7 serotypes (2008)**



Top panel: ages under 16 years; Bottom panel: all ages. Source: Reference Laboratory

**Figure 8. IPD incidence per 100,000 population that is covered by PCV10 and PCV13, incremental to the “residual” IPD incidence from PCV7 serotypes (2009)**



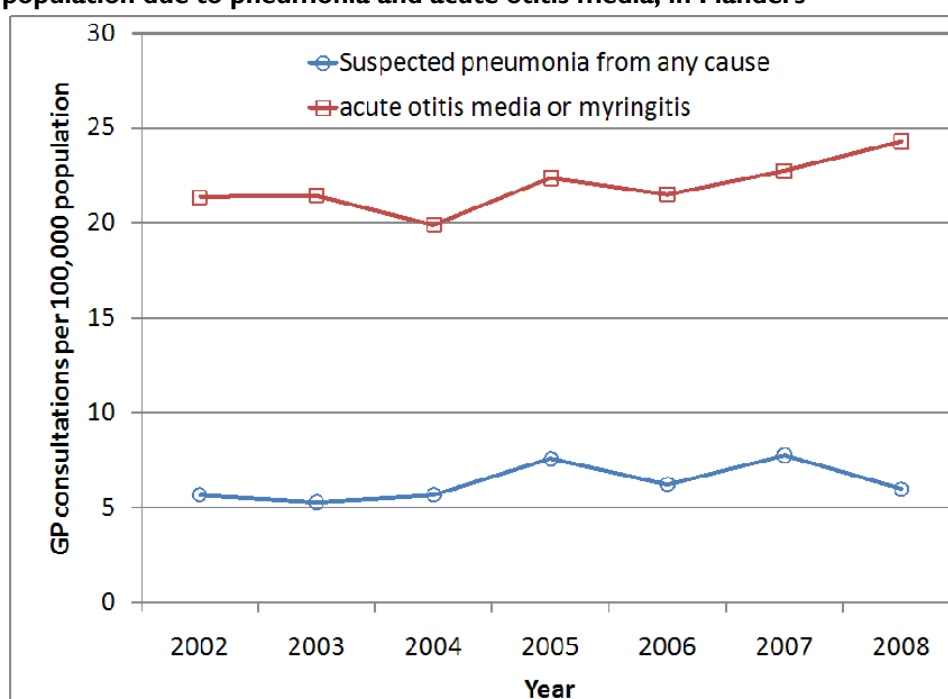
Top panel: ages under 16 years; Bottom panel: all ages. Source: Reference Laboratory

## 5.2 ACUTE OTITIS MEDIA (AOM) AND COMMUNITY ACQUIRED PNEUMONIAE (CAP)

PCV7 was expected to be effective against AOM and pneumonia. However, routine surveillance of the Flemish GP sentinel network “INTEGO” does not suggest evidence of any impact (year of increasing vaccine uptake). The INTEGO surveillance system collects data from about 55 GPs (not fixed per year), working in 47 practices, geographically spread over Flanders. To our knowledge, it is the only validated database that routinely contains incidence data on non-hospital consultations for these ailments. A limiting factor is that it covers only Flanders and not Wallonia and that patients who directly consult a paediatrician are not captured. The data presented here were not collected as part of a study to evaluate PCV7 impact and do not include data from paediatricians. It also covers only outpatient cases, and does not use a standardised clinical case definition nor uses radiological case definitions for pneumonia.

Figure 9 for AOM and suspected pneumonia over all ages shows that the incidence per 100,000 population has remained stable after the introduction of PCV7 in Belgium.

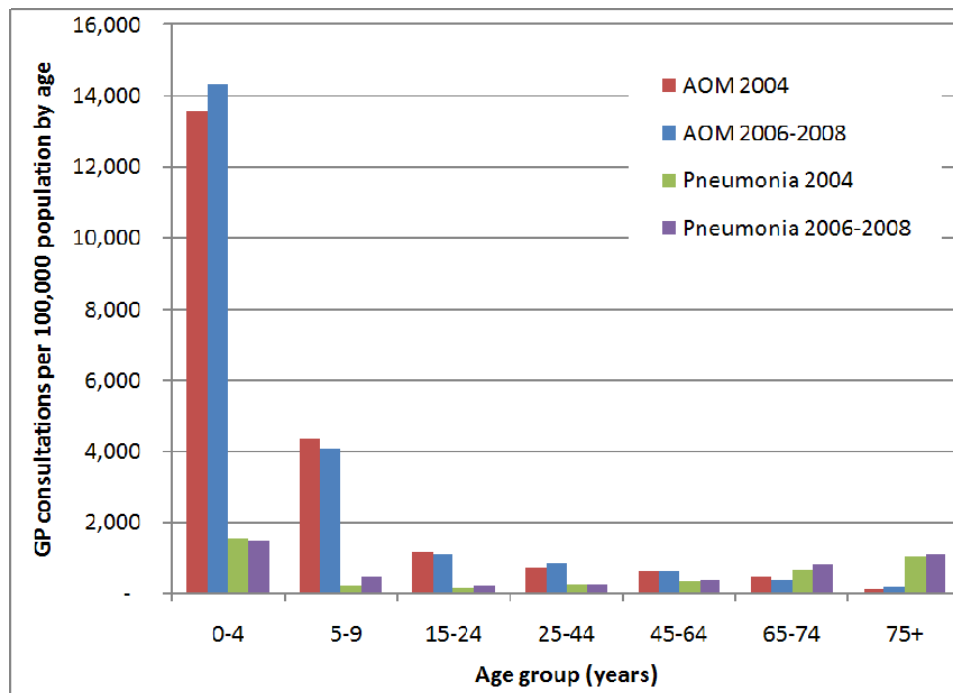
**Figure 9. Evolution of the incidence of GP consultations per 100,000 population due to pneumonia and acute otitis media, in Flanders**



Source: INTEGO

When we observe the age-specific incidence of AOM (Figure 10), we can speculate about the potential reductions PCV10 could produce in this incidence. What appears to be clear by comparing pre-PCV7 data (2004) with post-PCV7 data (averaged over 2006-2008) is that PCV7 had no impact on all-cause AOM GP consultations in the age group of 0-4 year olds, where since the introduction of PCV7, the incidence had slightly increased (instead of decreased by about 6% (see above)). It is important to keep in mind that this surveillance system was not designed to pick up specific impacts on AOM caused by *pneumococcus*. Since there are many serotypes for *pneumococcus* and other pathogens that can cause AOM, the scope for replacement effects seems to be greater than for the other clinical expressions of pneumococcal infections.

**Figure 10. Evolution of the age-specific incidence of GP consultations per 100,000 population due to acute otitis media and suspected pneumonia, in Flanders**



Source: INTEGO, 2004-2008

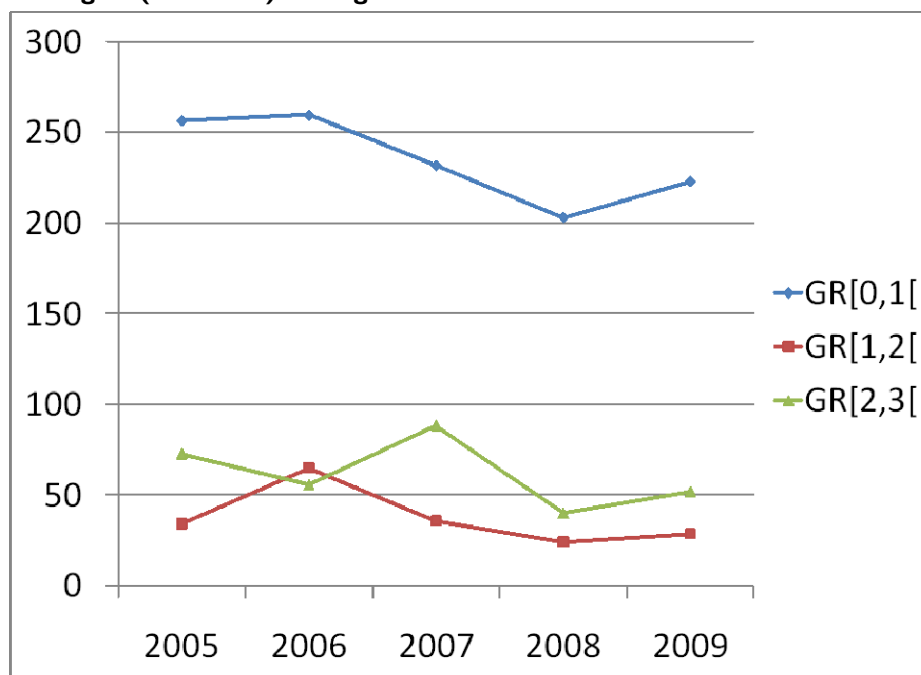
## 5.3 HOSPITALISATIONS

As explained above, in this section on the disease burden evolution in Belgium, we aimed to study the most recently available evolutions. These were not as up to date in the National database on hospital admissions, as in the alternative Carenet database we consulted in this subsection. We extracted information from the Carenet database for members of the Christian Mutualities (covering about 40% of the Belgian population). All extractions and analyses have been done on anonymised data at the medical direction of the Christian Mutualities, at all times under the supervision of a social insurance physician ('adviserend geneesheer'). At the time of data extraction and cleaning, Carenet contained information on hospitalisations until 2009. With about 90% of the hospitals included in this network, Carenet is being considered as representative of the Belgian population.

### 5.3.1 Meningitis hospitalisations

There is no clearly discernable pattern in the meningitis hospitalisations (all causes) recorded in Carenet, with the possible exception of the youngest age group (under the age of 1 year), in whom the incidence of meningitis hospitalisations steadily declined between 2005 and 2008, but rose again slightly to its 2007 level in 2009.

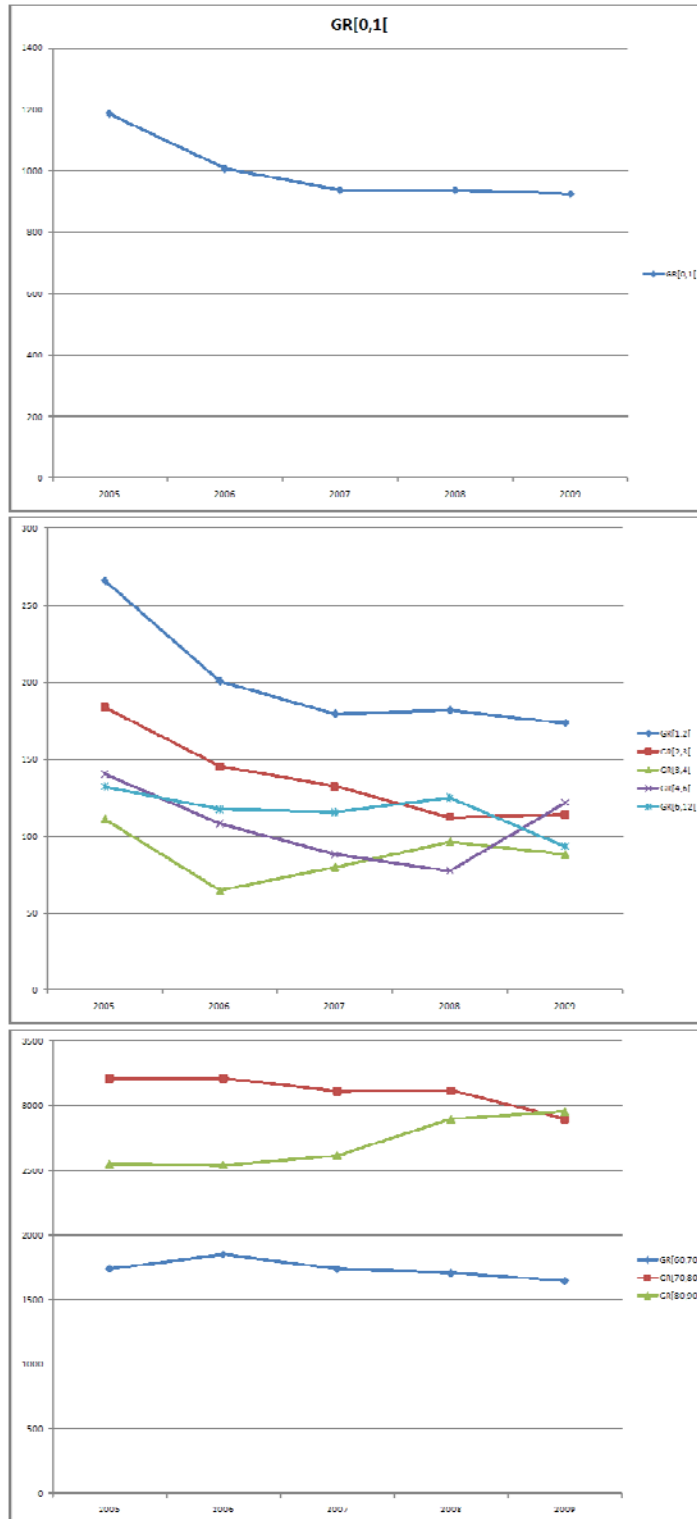
Figure 11. Incidence per 100,000 population of hospitalisations with meningitis (all causes) as diagnosis



Source: Carenet

### 5.3.2 Bacteremia and septicaemia hospitalisations

**Figure 12. Incidence per 100,000 population of hospitalisations for patients diagnosed with bacteremia and septicaemia, all causes (2005-2009)**



Source: Carenet

Figure 12 indicates that there appears to be a decline in hospitalisations for bacteremia in those aged between 0 - 1 years (top panel), 1 - 2 years and 2 - 3 years (middle panels). The only other discernable pattern seems to be that in the oldest age group, where the incidence increased (80-90 years, bottom panel).

### 5.3.3 Pneumonia hospitalisations

In terms of (all causes) hospitalisations with a diagnosis of pneumonia, there is no discernable trend, neither in overall incidence, nor in the age distribution during the years 2005-2009. This is the case for any pneumonia diagnosis, as well as for pneumonia as a primary diagnosis of the hospitalisation.

## 5.4 DEATHS

### 5.4.1 Invasive pneumococcal diseases (IPD) deaths

Through the Pedisurv network of the IPH we collected information on mortality for patients diagnosed with IPD. There were 1673 cases reported between January 2006 and December 2009 among children younger than 16 years. Information on outcome was available in 1072 cases (64%). Twenty-four children died (case fatality ratio of 2.2%) in this study period. Table 9 shows the evolution of deaths by age group. Children younger than 1 year died mostly following meningitis (73%) while in the older age groups shock, meningitis and complicated pneumonia were diagnosed. Table 9 shows a decrease during the first two years after widespread use of PCV7 in 2006-2007, but there was a rise again in 2009. Provisional data indicate that 3 children died in 2010 from pneumococcus.

**Table 9. Deaths following IPD in children < 16 years old**

Age	2006	2007	2008	2009	Total	(2010*)
[0, 1[	5	1	3	4	13	1
[1, 5[	6	1	1	1	9	0
[5, 16]	0	0	0	2	2	2
<b>Total</b>	11	2	4	7	24	3

\* Provisional data for 2010. Source: Pedisurv, IPH

Information on serotype was available for 20 cases. Serotype 7F was observed in 5 cases (25%), whereas serotype 19A and serotype 23F were each found in 3 cases. Table 10 presents the different serotypes by age group.

**Table 10. Serotype by age group in children < 16 years who died following IPD**

Serotype	Age			Total
	[0, 1[	[1, 5[	[5, 16]	
1	1	0	1	2
19A	2	1	0	3
19F	1	0	0	1
22F	0	1	0	1
23F	1	2	0	3
5	1	0	0	1
6B	1	1	0	2
7F	3	1	0	5
9V	1	1	0	2
<b>Total</b>	11	8	1	20

Source: Pedisurv, IPH

Information on an underlying risk factor for severe IPD was known in 16 of 24 cases and only present in 3 of these cases.

Case fatality ratios (CFR) for IPD in children aged <5 years vary significantly in Europe and ranged from 0.7% in Poland to 36.4% in Slovakia, with a mean CFR of 7.4%.<sup>158</sup> In Germany, the case fatality in children younger than 16 years was 4.9% and serotype 7F was associated with a higher risk of severe and fatal outcome than other serotypes.<sup>80</sup>

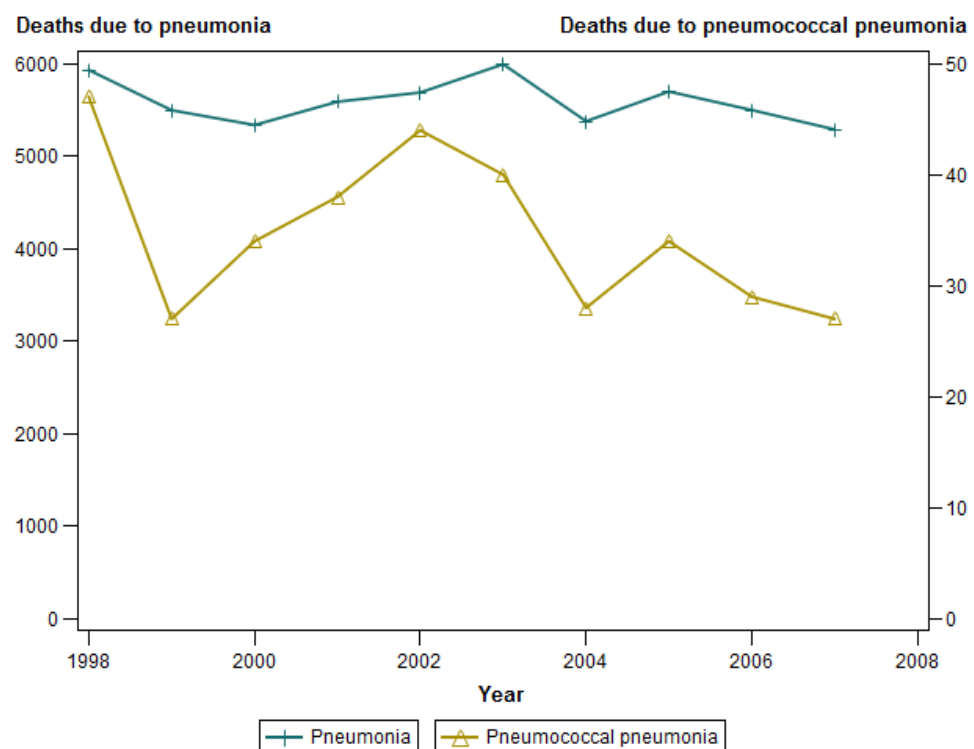
The broad range of CFRs may be related to differences in the patient populations captured by the various surveillance systems, differences in surveillance systems and, to a lesser extent, the differences in healthcare provision between the countries.

### 5.4.2 (Pneumococcal) pneumonia deaths

We also obtained information from the communities based on death certificates. As mortality data from Wallonia were incomplete, we focus on Flanders since these death registrations represent uninterrupted time series. However, these data were only available up to 2007 (i.e. at the start of the PCV7 vaccination programme).

Figure 13 shows the evolution of deaths with pneumonia and pneumococcal pneumonia as the immediate or underlying cause of death.

**Figure 13. Deaths with pneumonia and pneumococcal pneumonia as the immediate or underlying cause of death (plotted on left and right hand axis).**



Source: Death certificates, Flanders

### 5.4.3 Pneumococcal meningitis deaths

Table II lists the deaths in Flanders from pneumococcal meningitis, indicating that there has been an average of 1 death recorded per year in children 0-3 years of age, between 2002 and 2007.

**Table II. Deaths in Flanders with immediate or underlying cause recorded as pneumococcal meningitis**

Age	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	Total
[0,3[		2			1	1	1	1	1	1	8
6+	3	4	4	2	6	4	4	3	1	4	35
<b>Total</b>	<b>3</b>	<b>6</b>	<b>4</b>	<b>2</b>	<b>7</b>	<b>5</b>	<b>5</b>	<b>4</b>	<b>2</b>	<b>5</b>	<b>43</b>



#### 5.4.4 Pneumococcal septicaemia deaths

Table 12 shows deaths attributable to pneumococcal septicaemia, based on the death certificate codings.

**Table 12. Deaths in Flanders with immediate or underlying cause recorded as pneumococcal septicaemia**

Age	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	Total
[0, 6[	1	1					2				4
[20, 50[		2	1	1	4	2	2	3	2	1	18
[50, 60[	1	1	2	1	3	5		3	3	3	22
[60, 70[	3	4	3	4	6	3	6	3	2	4	38
[70, 80[	7	3	5	3	15	8	8	6	4	7	66
[80, 90[	6	4	5	9	10	3	8	11	5	8	69
90+	3	1	3	1	5	4	4	3	2	3	29
<b>Total</b>	21	16	19	19	43	25	30	29	18	26	246

## 6 ECONOMIC EVALUATIONS OF PCV10 AND PCV13

A detailed review of economic evaluations predating 2006 is available in Beutels et al.<sup>159</sup> More recent reviews of economic evaluations on PCVs are available, although they each focus on just one particular aspect, such as otitis media<sup>160</sup>, herd immunity<sup>161</sup>, studies from one country<sup>162</sup>, or a small group of countries.<sup>163</sup>

By using the combined search string “economic OR cost-effectiveness OR cost-benefit OR cost-utility OR cost-effectiveness OR cost-benefit OR cost-utility” in our merged database (Figure 1) we identified 38 economic evaluations published since 2006 (excluding meeting abstracts, reviews and cost studies). About 75% of these (or 28 publications) were on PCV7.<sup>5 164-190</sup>

In addition to the above 28 cited studies on PCV7, one study estimated the costs and benefits of PCV13 versus PCV7<sup>191</sup>, and four others estimated the costs and benefits of PCV10 versus PCV7.<sup>192-195</sup> One additional study focused on a novel model to estimate outcomes of PCV10 versus PCV7 while implying vaccination costs would remain the same.<sup>196</sup> Of greater interest than the singular PCV10 and PCV13 studies are four studies, which considered both new vaccine candidates in their analysis.<sup>181 197-199</sup>

We discuss the English language publications (excluding<sup>193 199</sup>) on PCV10 and PCV13 in the next section, in some more detail.

### 6.1 MODELS STRUCTURE

The state of the art of economic evaluation on this subject is to use a static population model to calculate the net indirect effects (of herd immunity and serotype replacement) and either or not combine this with a static cohort model to calculate the direct effects in a single ageing cohort. The combination of a cohort model and a static population model is also the approach that was used by Beutels et al in the 2006 KCE report on pneumococcal vaccination.<sup>4</sup> In structural sensitivity analyses, Beutels et al<sup>4</sup> also modelled the entire population over time (i.e. multiple cohorts), using the 5 years post-PCV7 herd immunity and serotype replacement estimates for the US experience, based on Ray et al.<sup>200</sup> They showed that the difference between these approaches was virtually negligible.

None of the published economic evaluations to date have applied a dynamic transmission model to estimate the cost-effectiveness of PCVs. Differences in their results are therefore mainly driven by the input data they used.

A notable exception is one group of studies on PCV10<sup>195 197</sup>, which use a “steady-state static population model” based on a model by De Wals et al<sup>196</sup>, assuming that the direct and indirect herd effects of different vaccination options can be estimated over a one year time period from a steady state year in the future, for the total population. It is not clear how the steady state is implicitly defined in these models (i.e. how far in the future the steady state is assumed to be, though implicitly the assumption seems to be that it is reached for PCV7, up to the point where observational data exist). The authors of these studies assert that their approach renders discounting of future costs or effects unnecessary, because they evaluate the cost-effectiveness over a one year period, from the steady state year to the steady state year+1. That is, the future outcomes earned by a series of previously vaccinated cohorts are balanced against the costs of vaccinating a cohort in the present. Yet, the decision maker is investing in the first vaccinated cohort many years before the steady state year. Hence, it is difficult to disentangle time preference effects under this approach. Even if time preference up to the steady state year would not need to be accounted for, by assuming that the steady state year represents an average year in the present, these analyses estimate the number of life-years and quality-adjusted life-years (QALYs) foregone due to mortality in the one year time period between the steady state year and the steady state year+1.

It is incorrect (vis-à-vis current practice of discounting for other health care interventions) to assume that such a future stream of life years should not be discounted back to the steady state year, even if one assumes implicitly that the steady state year is considered as an average year in the present. It is of note that Chaiyakunapruk et al<sup>201</sup> recently made a comparison of PCV7 models, which includes a 2009 version of this steady-state static population model as implemented by GSK (“Supremes”), and some of the more widely used models (combining a birth cohort with a static population model to assess herd immunity). These comparisons show that it is precisely to case-fatality assumptions (and hence life-expectancy) that the steady state model is most sensitive. Hence comparisons between this group of model-based analyses and other approaches should be interpreted with care.

## 6.2 MAIN ASSUMPTIONS AND RESULTS

Since in this report we are interested in PCVs of higher valency, we will not discuss all the PCV7 analyses<sup>5 164-190</sup> individually. Many of these were conceptually not substantially different from the PCV7 analysis in the 2006 KCE report.<sup>4</sup> Some of these can be categorised (as in Beutels et al<sup>4</sup> for pre-2006 studies) as irrelevant, since they did not adapt to local serotype distribution and/or did not explore the interplay between the herd immunity effects and serotype replacement and/or did not compare different vaccination schedules. However, some of these publications confirmed and emphasised, as Beutels et al<sup>4</sup> also elaborated in the 2006 KCE report, that the assumed extent of the herd immunity effects and serotype replacement are highly influential, and that the 2+1 schedule dominates the 3+1 schedule, under equally assumed herd immunity effects after the booster dose. A major limitation of these PCV7 analyses is that they were usually based on the US observations regarding herd immunity and serotype replacement. Although it has been amply demonstrated by Ray et al<sup>200</sup> after 5 years and Ray et al<sup>180</sup> after seven years that the net indirect effects were beneficial in the US (with a very cost-effective or even cost saving PCV7 programme as a result), as outlined in section 4.1 above, the net impact of PCV7 on IPD has been different in Europe.

Regarding the other analyses on PCV10 and PCV13, the first striking difference is the wide variety in assumed vaccine prices and the lack of scenario analyses with vaccination costs. This was previously shown to be highly influential.

Furthermore, none of the studies adjusted the direct vaccine effectiveness by serotype immunogenicity, making the assumption that the additional effectiveness on IPD caused by the additional serotypes would be the same as (sometimes the average) for the 7 serotypes in PCV7 (as shown in Table 13, most assumed this to be 94% for the additional serotypes). Studies attempting to estimate the effects on AOM and pneumonia have assumed that the distribution of IPD serotypes represents well the serotype distribution found in patients with AOM and pneumonia (see also below).

Since the effectiveness of PCV10 against AOM remained largely unexplored, head-to-head analyses tended to conclude that PCV13 was more cost-effective than PCV10 (though Chuck et al<sup>197</sup> noted this is reversed, if they assumed an effect on NTHI AOM).

The influence of including or excluding cross reactive serotypes is rarely explored. In Talbird et al<sup>195 203</sup> cross-protection as estimated by Whitney et al<sup>15</sup> for PCV7 was included for 19A and 6A, but the influence of this assumption was not explored.

In the 2006 KCE report, Beutels et al<sup>4</sup> used 3 different sets of QALY/DALY estimates (with negligible differences in impact). These sets were also used by the economic evaluations in Table 13 (see below, section model input data). Estimates of quality of life as used by O'Brien et al<sup>192</sup>, stem from an earlier study by Prosser et al<sup>205</sup> which produced estimates that are very high by comparison to other studies, due to their approach (as previously discussed in Beutels & Viney<sup>206</sup>).

Table 13. Main assumptions and results of economic evaluations on PCV10 or PCV13

First author, country, year	Vaccination costs per dose schedule	Model	Main effectiveness assumptions	Results
O'Brien <sup>192</sup> , US, 2009	PCV7=€45.6 PCV11=€70.5  3+1 schedule	Markov state transition model	Effectiveness versus AOM, PCV11 vs. PCV7: - 4-24 months: 28% vs. 6.4% - 25-36 months: 14% vs. 3.2% - 37-48 months: 7% vs. 1.6% IPD and pneumonia effectiveness as for PCV7 in Lieu et al, 2000 <sup>202</sup>	Cost-saving with savings from AOM outweighing savings from other pneumococcal disease (includes indirect costs of parental time and QALY losses of parents)
Chuck <sup>197</sup> , Alberta, 2010	PCV7 =PCV10 =PCV13 = €51 3+1 schedule	Steady-state population model	97.4% against additional serotypes (no cross protection) 3% or 5% <sup>a</sup> for AOM with NTHI	PCV13 dominates PCV10 (but reversed if effectiveness against NTHI AOM is included)
Rozenbaum <sup>181</sup> , Netherlands, 2010	PCV7 = €50 PCV10=€62.25 <sup>b</sup> PCV13 = €74.5  3+1 schedule	Cohort model	97.4% against additional serotypes (no cross protection) Net indirect effects of PCV10 = PCV13 = 10% No effect on NTHI AOM Pneumonia and AOM estimates: same as PCV7 (adjusted for additional IPD serotypes)	PCV10 vs. PCV7: €52,947 per QALY gained PCV13 vs. PCV7: €50,042 per QALY gained
Rubin <sup>191</sup> , US, 2010	PCV7 = €51.6 PCV13 = €70.7  3+1 schedule	Markov state transition model	94% against IPD additional serotypes (no cross protection) 7.3% against suspected pneumonia 12.9-22% against hospitalised 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: €2404 per QALY gained Catch up 16-35m: €17,715 per QALY gained Catch up 16-59m: €52,028 per QALY gained
Talbird, <sup>195 203</sup> , Canada, Germany, Mexico, Norway, 2010	PCV7=PCV10  3+1 schedule 2+1 schedule  Country dependent	Steady-state population model	IPD schedule effectiveness and serotype specific effectiveness (based on Whitney <sup>15</sup> including cross protection (6A, 19A) + 94% against additional PCV10 serotypes). Herd immunity for IPD (PCV10=PCV7): - < 5years: 15.4% - ≥ 5years: 29% All-cause pneumonia: - Hospitalised: 25.0% vs. 20.5% (PCV10 vs. PCV7) - Non-hospitalised: 4.3% (PCV10=PCV7) AOM due to VT: 57.6% vs. 57.2% (PCV10 vs. PCV7) AOM due to NTHI: -11% vs. +35.6% (PCV10 vs. PCV7)	PCV10 vs. PCV7: cost-saving

First author, country, year	Vaccination costs per dose schedule	Model	Main effectiveness assumptions	Results
			All-cause AOM: 6.7% vs. 22.9% (PCV10 vs. PCV7)	
Sartori <sup>194</sup> , Brazil, 2010	PCV10=€11.3 3+1 schedule	ProVac model (25 cohort model) <sup>204</sup>	94% against vaccine serotypes (no cross protection) for 5 years AOM due to VT: 57% Pneumonia due to VT: 87.5%	PCV10 vs. PCV7 in high risk children: €9,392 per DALY averted
Kim <sup>198</sup> , The Gambia, 2010	PCV7= PCV10= PCV13= €2.5 3+0 schedule	Markov cohort model	(All-cause) primary endpoint pneumonia: - PCV7: 26% - PCV10: 35% - PCV13: 41% Pneumococcal meningitis/sepsis: - PCV7: 16% - PCV10: 22% - PCV13: 26% AOM impact excluded Herd immunity, serotype replacement explored in sensitivity analysis	All PCVs considered cost-effective (costs per DALY averted < 3xGDP/capita)  PCV13 more cost-effective than PCV10, and PCV7

a. Unclear due to conflicting statements

b. Average between PCV7 and PCV13

AOM: acute otitis media, VT: vaccine type; NTHI: non-typable *Haemophilus influenzae*; IPD: invasive pneumococcal disease; CAP: community acquired pneumonia; QALY: quality-adjusted life-year; DALY: disability-adjusted life-year; GDP: gross domestic product

## 7 MATHEMATICAL MODELS OF PNEUMOCOCCAL TRANSMISSION

Our search identified 11 different publications<sup>207-218</sup>, which presented or discussed mathematical models without being coupled to economic evaluation.

None of these models apply to PCV10 or PCV13. Interestingly, Van Effelterre et al<sup>208</sup> focused on the interaction between ecological pressures from PCV7 vaccination and antibiotic use to explain the rising incidence of serotype 19A in the US. This model is designed to generate hypotheses leading to a better understanding of mechanisms. Only two other models represent an application to the transmission dynamics of PCV7<sup>213 218</sup>, with the remainder discussing or comparing different static models<sup>210 211 216 217</sup>, or demonstrating specific transmission dynamic features of pneumococci in theory<sup>207 209 212 214 215</sup>, like previous pre-2006 models did as well.<sup>219 220</sup>

Melegaro et al<sup>213</sup> and Snedecor et al<sup>218</sup> are the only publications that tried to quantify the impact of the PCV7 at the level of the population. They both developed an age structured compartmental deterministic model. Snedecor et al<sup>218</sup> did not distinguish vaccine serotypes from non-vaccine serotypes. Their approach focused on reproducing the observed herd immunity impact in the US (and exploring the likely impact of different vaccine uptake scenarios), by distinguishing IPD and nasopharyngeal carriage as pneumococcal infection states. Snedecor's et al approach did not allow to account for serotype replacement. In order to fit the observed data on herd immunity (US, 2000-2005), they departed from the mass action principle used widely in transmission dynamic modelling and defined the force of infection in the oldest age group to be proportional to the squared number of carriers in the youngest age group.

The more recent model by Melegaro et al, is able to cope better with some of these methodological challenges. In Melegaro et al<sup>213</sup> serotypes are grouped in either PCV7 vaccine type or PCV7 non-vaccine type groups. They made projections of different PCV7 vaccination strategies and used the following datasets:

1. Longitudinal pneumococcal carriage data from nearly 500 individuals of all ages in England and Wales. These data were used to estimate the force of infection of vaccine serotypes and non-vaccine serotypes.
2. Age specific IPD incidence data by serotype (all ages) from the national surveillance system in England and Wales. In combination with the previous dataset, these data were used to derive case:carrier ratios.
3. The degree and duration of vaccine effectiveness, as well as the level of competition between vaccine and nonvaccine serotypes was derived from US IPD incidence and vaccine uptake data during the pre- and post-vaccination era (1998-2004). The transmission model was fitted to the incidence data (after deriving age-specific mixing patterns from them), by modifying the combination of parameters expressing the age-specific duration of carriage (assumed to be independent of serotype), the degree and duration of vaccine protection against carriage of vaccine and non-vaccine serotypes, as well as the level of competition between these groups of serotypes (and keeping the likely most suitable mixing patterns, derived separately, and vaccine uptake estimates fixed).

After the main parameter sets were decided on, projections were made for England and Wales suggesting that vaccine type pneumococci would be eliminated over a 5 to 10 year time period, but exhibiting at the same time high sensitivity to the parameter values that express competition between vaccine and non-vaccine serotypes.

As expected, the duration to elimination of vaccine types is shorter with more expansive catch-up programmes (to age 60 months). The predictions related to non-vaccine types remained much more speculative and highly sensitive to the selection of fitted parameter sets for carriage duration, the force of infection of and competition between vaccine types and non-vaccine types. The latter is also the main uncertainty in observational studies, and Melegaro et al duly noted that estimates of replacement effects are affected “by secular trends in prevalence and antimicrobial sensitivity of

serotypes at the time of introduction, differences in surveillance systems, differences in clinical practice". None of these aspects could be taken into account in their study.

In addition to the limitation that the approach requires to calibrate the model by changing many different parameters simultaneously (and hence the options for fitting are tremendously large, despite the fact that social mixing is kept constant), they discussed the following main limitations of their projections:

1. They included serotype 6A in the PCV7 vaccine type group (because of the observed cross protection), but this was using data from the time before 6C and 6D had been identified, and this may affect the fittings and projections.
2. They grouped all serotypes in two main groups, while there exists considerable heterogeneity between different serotypes in each group (e.g., transmissibility, duration of carriage, ability to co-colonise, ability to prevent co-colonisation with other serotypes, ability to cause disease).

Despite that Melegaro et al<sup>213</sup> have made impressive progress in this area for PCV7 (their main aim is to support projections for policy in developing countries), in the current policy supporting report we chose not to undertake the first dynamic transmission model approach of PCV10 or PCV13 for four main reasons:

1. While we have data for Belgium on carriage of pneumococci in children (from one cross sectional study in day care centres pre-PCV7 introduction<sup>221</sup>, and one cohort study in Brussels' schools during the period of PCV7 introduction (2006-2008)<sup>222</sup>), this is currently lacking for the general population in Belgium.
2. The IPD incidence data for Belgium were not available by serotype for adults at the start of our study (only in children). Data on serotype-specific IPD in adults over 50 years of age have become recently available to us (2011).
3. We believe that a number of fundamental aspects of colonisation, carriage and transmission of pneumococci are still poorly understood, such that the role of transmission models would be more to help understand and generate hypotheses, rather than to make projections to support policy making. For the latter, our lack of understanding basic mechanisms to model transmission and colonisation undermines our ability to quantify or even identify uncertainties that are embedded in these types of projections.
4. Last but not least, in order to undertake such a complex modelling study, we would require research capacity that surpasses the time and resources typically available to undertake an individual KCE report.

As a research agenda to enable and improve dynamic models for pneumococci, we propose the following:

1. Apply Melegaro et al's approach for calibration to different European countries instead of the US (in Melegaro et al<sup>213</sup>, the model is fitted to US data, and hence the implicit assumptions of their model (e.g., regarding antibiotic use) are assumed to be transferable to England and Wales).
2. Develop laboratory techniques that can detect carriage of multiple serotypes from nasal aspiration or swaps.
3. Undertake a representative general population study in Belgium (oversampling children, preferably sampling full households) to obtain pneumococcal carriage information (e.g. by nasopharyngeal swaps or aspiration) at regular intervals over a period of a year. Ideally techniques would be available to detect multiple serotypes being carried simultaneously
4. Enhance IPD surveillance, as already done in children, such that (at least over the same period as above) IPD cases of all ages are serotyped (also including multiple serotypes), and clinical information and antibiotic susceptibility of serotypes is determined
5. Provide long term support to undertake and build capacity in basic research in mathematical modelling of infectious diseases in humans

## 8 COST-UTILITY ANALYSIS OF PCV10 AND PCV13 IN BELGIUM

The general principles of this analysis are that we parameterise the uncertainty we can parameterise using distributions, and that we model distributions and present the results as distributions. We explore the assumptions we make in order to do this. We show all outcomes separately for IPD (distinguishing meningitis, bacteremia and other IPD), otitis media and pneumonia. We show all results for different levels of protection offered by PCV10 against AOM, distinguishing between AOM caused by Non Typable *Haemophilus Influenzae* (NTHI) and all-cause AOM. We show all results with and without herd immunity, and we explore the impact of serotype replacement. We perform multivariate threshold analysis on price differences between different vaccine formulations. We show the impact on effectiveness and cost-effectiveness of using three different interpretations regarding the correlates of protection for the efficacy of PCV10 and PCV13, and show the impact of including or removing individual serotypes for which protection can be contested. In order to be able to do this, we needed to develop a flexible model that can incorporate probabilistic sensitivity analysis. As explained in the review section on mathematical models, for various reasons we opted to attempt this by using a static model, in which herd immunity and serotype replacement is imposed rather than estimated through the dynamics of transmission of pathogens. We do not include the impact vaccination may have on preventing antibiotic resistance.

### 8.1 STUDY DESIGN

#### 8.1.1 General

Data analyses and simulations were performed using MS Excel 2007, @Risk 4.5 and SAS.

The baseline costing perspective is that of the Belgian health care payer, which includes collective payments by the Belgian health care system, as well as co-payments for health care by patients. All cost data are expressed in Euro 2010. Our primary measure of relative efficiency is direct costs per Quality-Adjusted Life-Year (QALY), though a wider range of health outcomes is presented in incremental cost-effectiveness analyses. Time preference is accounted for by discounting costs at an annual constant rate of 3%, and effects at 1.5%. These analytical choices are in line with the Belgian guidelines for economic evaluation in health care<sup>223</sup> and an international WHO guide on economic evaluations of vaccines.<sup>224</sup>

#### 8.1.2 Vaccination options

The options for vaccination were selected based on global experience with PCV7, as well as the results from clinical trials with PCV10 and PCV13 (see sections 4.2 and 4.3 above). Given the routine Belgian infant vaccination schedule and the fact that PCV10 is only licensed under a 3+1 schedule, we focus on the following options in our analysis:

- Option 1: Current situation. PCV7 vaccination using a 2+1 schedule with injections at 2, 4 and 12 months of age.
- Option 2: PCV10 vaccination using a 3+1 schedule with injections at 2, 3, 4 and 12 months of age. In addition, the 2+1 schedule has been considered, in anticipation of potential changes in the authorized schedule.
- Option 3: PCV13 vaccination using either a 2+1 or 3+1 schedule with injections at 2, (3), 4 and 12 months of age.

Options 2 and 3 are compared to option 1, as well as incrementally to each other.



### 8.1.3 Mathematical model structure

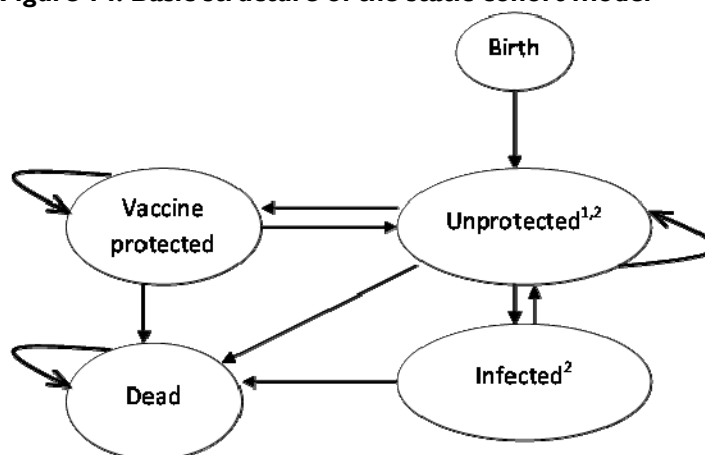
The economic analysis is by necessity based on a mathematical simulation model. We have opted for an integrated model, which combines two submodels, and can be subjected to multivariate probabilistic sensitivity analysis.

#### 8.1.3.1 *Static cohort model without herd immunity*

An age-structured “classic” Markov model was developed in MS Excel, simulating costs and effects of pneumococcal disease and vaccination in a single closed Belgian cohort followed from birth until 100 years of age.

The first 6 years of the model run in monthly cycles. The following 94 years run in annual cycles. The model is flexible in that any 1 to 4 dose schedule can be assumed over the 100 year time span (and the time span can be adjusted), and specific in that in under 6 year olds, the timing of each dose can be focused on any month. This model is static, so like all the other models used for economic evaluation on pneumococcal conjugate vaccines (see section 6 above), it does not generate herd immunity effects, based on built-in transmission dynamics.

**Figure 14. Basic structure of the static cohort model**



1 Not vaccinated, or vaccinated but not (or no longer) protected

2 Modelled in separate states (and with separate transitions from and to other states) for IPD, all-cause pneumonia and all-cause otitis media (detail not shown for clarity).

#### 8.1.3.2 *Static population model to assess indirect effects for PCVs*

Based on observations in the USA and Belgium, the indirect effects (of herd immunity and serotype replacement) are simulated (and their consequences in terms of costs and effects) in a static population model. This population model assesses one year of infections over the entire population to simulate herd immunity and serotype replacement at the population level.

Herd immunity effects for PCV as estimated in the static population model are looped back into the static cohort model, so that in fact both submodels form one integrated model. This implies also that sensitivity analysis is performed on the integrated model. Since the impacts of herd immunity and serotype replacement are highly speculative the uncertainty around these aspects are not only parameterised in the models, but are also elaborated in scenario analyses (see results section 8.3).

As recommended by international guidelines for the economic evaluation of vaccination programmes<sup>224 225</sup>, the time span is chosen during the analysis such that the median ICERs reach a plateau. In the current report the focus is on a 5 year time span for incurring infections, and a lifelong time horizon for infected persons incurring long term consequences (sequelae including death) from their infections. Alternative calculations using a 10 year time span are also shown in sensitivity analyses.

## 8.2 MODEL INPUT DATA

### 8.2.1 Epidemiological parameters and transition probabilities

The incidence of invasive pneumococcal disease (IPD) was based on the latest available Belgian data (for the year 2009) on IPD from the National Reference Laboratory, in collaboration with the Pedisurv project of the IPH for children under 16 years<sup>226</sup>, and in collaboration with Pfizer for adults over 50 years of age.<sup>227</sup> For adults between 16 and 50 years of age we used the 2009 serogroup data from the National Reference Laboratory, adjusted for serotypes contributing to these serogroups, as observed for the age groups for whom serotype data are available (as shown in figure 8, bottom panel). The latter approach was also used in the 2006 KCE report for adult age groups.

Additionally hospitalisation rates for bacteremia, other IPD, suspected pneumonia, otitis media and the proportion of these that end in death were obtained from the National Hospital Database (RCM/MKG) from the pre-PCV7 period (since these aspects are unlikely to have changed after inspection of the evolution of cases in the carenet database for the most recent years). For bacteremia and other IPD, these data are only used for ages >16 years, and thus affect only the estimates with herd immunity included (these are in agreement with recent data on mortality in adults with IPD that became recently available). For pneumonia and otitis media, hospitalisation rates are used to assign age-specific health care costs (estimated based on direct surveys, see below) to hospitalised versus non-hospitalised cases of pneumonia and otitis media (see below), and to estimate mortality from all-cause pneumonia. All these estimates were assigned age-specific beta distributions.

Table 14a. Model input data related to population and disease burden

Parameter	Values					Distribution	Source
Population of Belgium, all-cause mortality and life-expectancy by age	Age-specific (2007), with cohort of 121,006 newborns <sup>a</sup>					NA	FOD Economie, KMO, Middenstand en energie
Serotype distribution IPD, latest available (2009)	Age-specific: all ages See tables 6, 7 and 8 and figure 8					Beta (age-specific)	NRL, IPH, Pfizer
Incidence of IPD, adjusted for underreporting	Age-specific, see figure 8					Beta (age-specific)	NRL, IPH / Pedisurv
Proportion of IPD causing meningitis, bacteremia and others	Assumes meningitis and shock diagnoses are known, while unknowns are distributed only over the other diagnoses					Beta(age-specific)	Pedisurv, IPH (2006-2009)
		<1	[1,2[	[2,5[	[5,16[		
	Meningitis	22.3%	8.9%	2.2%	3.8%		
	Bacteremia	55.6%	56.1%	31.8%	16.5%		
	Other	22.1%	35.0%	66.1%	79.8%		
Case-Fatality Ratios		<1	[1,2[	[2,5[	[5,16[	Beta (age-specific)	Pedisurv, IPH (2006-2009)
	Meningitis	10.7%	11.1%	2.8%	2.8%		
	Bacteremia	0.8%	1.8%	0.8%	3.3%		
	Other	0.3%	0.3%	0.3%	0.3%		
Acute otitis media, GP consultations Suspected pneumonia, GP consultations	Age-specific: See figure 10					Beta (age-specific)	Intego
Proportion of meningitis	14% (71% severe bilateral) 16% (40% severe)					Beta (age-specific)	Melegaro et al, 2004 <sup>228</sup> Jit M, 2010 <sup>229</sup>
- Hearing deficits							
- Neurological deficits							

<sup>a</sup> Note: there is a discrepancy between the January 2008 birth cohort reported by FOD Economie, KMO, Middenstand en energie as part of the total population structure, and the latest estimated birth cohort (April 2011: 228,049). We use the latest year for which the population structure is available at each age in years. This number has only (marginal) relevance for disease burden and budget-impact estimates, not for cost-effectiveness calculations. NRL: National Reference Laboratory, IPH: Scientific Institute of Public Health.

**Table 14b. Annual hospitalisation rate per 100,000 population based on the National Hospital Database (RCM/MKG)**

Age (years)	Pneumococcal meningitis	Pneumococcal septicaemia	All-cause pneumonia	Acute Otitis Media (AOM)
<1	33.1	45.7	1,161	339
1-4	2.9	14.3	912	230
5-9	0.9	1.8	211	75
10-14	0.4	0.6	63	11
15-19	0.3	0.5	47	3
20-24	0.5	0.4	43	2
25-44	0.4	0.9	67	2
45-64	0.9	1.9	145	1
65-74	1.3	5.0	413	2
75+	1.0	10.3	1,362	1

Based on RCM/MKG(2001-2004), with following ICD-9 CM codes in first diagnostic field: Pneumococcal meningitis: 320.1; Pneumococcal septicaemia: 038.2; Pneumococcal pneumonia: 481; All cause pneumonia: 481+ 482.9 + 485 + 486; Acute otitis media: 38100+38101+38102+38103+38104+38105+38151+38200+38201+38202

**Table 14c. Fatalities proportionate to hospitalised cases, of the same category (case\*-fatality ratio)**

Age (years)	Pneumococcal meningitis	Pneumococcal septicemia	All-cause pneumonia	Pneumococcal pneumonia
<1	6.6%	1.0%	0.04%	0.04%
1-4	11.3%	0.0%	0.00%	0.01%
5-9	4.5%	2.3%	0.02%	0.02%
10-14	0.0%	0.0%	0.13%	0.00%
15-19	12.5%	0.0%	0.00%	0.00%
20-24	7.7%	0.0%	0.18%	0.00%
25-44	6.1%	12.5%	0.30%	0.21%
45-64	10.3%	17.9%	1.38%	0.46%
65-74	17.6%	15.9%	2.43%	0.85%
75+	31.3%	27.1%	4.78%	1.16%

Based on RCM/MKG(2001-2004), with following ICD-9 codes in first diagnostic field: Pneumococcal meningitis: 320.1; Pneumococcal septicaemia: 038.2; Pneumococcal pneumonia: 481; All cause pneumonia: 481+ 482.9 + 485 + 486; \* note that all meningitis and septicaemia cases can be assumed to be hospitalised , but not all pneumonia cases.

## 8.2.2 Vaccine efficacy estimates

### 8.2.2.1 Vaccine efficacy estimates against IPD

No data on clinical efficacy of PCV10 and PCV13 were available, with the exception of PCV10 efficacy on pneumonia. The data used to estimate vaccine efficacy against IPD are given in tables 15-19. These are the serotype specific data (ELISA and OPA titres) of the different vaccines and relevant schedules. We identified for each vaccine the schedules that concurred best with the current infant vaccination schedule in Belgium (i.e. administration opportunities at months 2, 3, 4 and 12, with the current PCV7 schedule being at months 2, 4 and 12), keeping in mind that we need information on both PCV10 or PCV13 and PCV7 in the same trial setting. For PCV10 this is best represented in the Vesikari et al<sup>106</sup> publication for a 3 dose priming course and in the Wysocki et al<sup>105</sup> publication for a 2 dose priming course. For PCV13, we identified the trials published by Kieninger et al<sup>153</sup> and Gadzinowski et al<sup>150</sup> for 3 dose priming schedules and Snape et al<sup>151</sup> for a 2 dose priming schedule.

The Kieninger<sup>153</sup> and Snape<sup>151</sup> trial results are adjusted by unpublished trial 009 (Elisa data only) and the Gadzinowsky trial results to account for potentially lower immune responses in the mass produced PCV13 formulation and the inclusion of polysorbate 80.

We use a similar methodology as outlined in Hausdorff et al<sup>230</sup> to scale the serotype specific immunogenicity data with the serotype specific observational effectiveness data. This methodology is based on the primary course immunoresponses only. That is, ELISA and OPA immunoresponses for serotypes common with PCV7 (including serotype 6A), are scaled according to the ratio between PCV10 or PCV13 versus PCV7, and multiplied by the serotype specific effectiveness estimated in the pivotal case-control control study by Whitney et al.<sup>15</sup>

For additional serotypes (i.e. not common with PCV7), the difference in immunoresponse is taken as the serotype-specific response. For serotype 19A, we have also made the same basic assumption as Hausdorff et al<sup>230</sup>, namely that the nominal value observed in the trials for PCV10 and PCV13 applies.

We attempted to also account for lower observed immunoresponses for PCV13 in its mass produced version, which contains polysorbate 80 (not present in the version tested in the pivotal trials). Based on information from clinical trial 009, reported by EMA (only data on ELISA),<sup>231</sup> we adjusted the ELISA-based estimates using the Hausdorff methodology by the ratio between results with and without polysorbate 80, as produced in the head-to-head comparison of trial 009. Similarly, we adjusted the OPA estimates obtained by the ratio between the Gadzinowski<sup>150</sup> (contained polysorbate 80, but made no comparison without polysorbate 80 or PCV7) and Kieninger<sup>153</sup> trial (did not contain polysorbate 80, but compared with PCV7) results, which used the same vaccination schedule.

As in Hausdorff et al<sup>230</sup>, all adjusted values are constrained to have a maximum of 100%. In addition to Hausdorff et al<sup>230</sup>, we introduce the constraint that, in the interest of comparative analyses, the finally obtained estimate for 2 priming doses should not exceed that of 3 priming doses for any given serotype.

As outlined in the review section above, virtually all economic evaluations on PCV10 or PCV13 to date have assumed that all additional serotypes would have the same average effectiveness as observed for common PCV7 serotypes in the US (i.e. 92.4% or 94.7% depending on whether they averaged including serotype 6A or not, respectively). Henceforth, we will refer to this as the “average” approach for effectiveness. To our knowledge the impact of scaling these observational effectiveness estimates according to ELISA or OPA immune response levels has not been explored in the context of economic evaluations on this subject.

This is why we compare our cost-effectiveness results using different approaches to interpret PCV vaccine efficacy. When using the average approach, we make for PCV10 different assumptions about protection against serotype 19A (if included, we assume it induces the same level of cross protection as observed in Whitney et al<sup>15</sup>), and for PCV13 about protection against serotype 3 (if included we use the average effectiveness of the other serotypes directly common between PCV7 and PCV13 (i.e. excluding serotype 6A), as reported by Whitney et al<sup>15</sup>). When using the scaled ELISA and OPA measures we use the estimates shown in tables 16 and 19 below. Note that in our approach we are following the argumentation of PCV10's producer, in that the test they developed would yield equivalent ELISA values as the WHO standard (hence the cut off for PCV10 at 0.2 µg/ml for PCV10 and 0.35 µg/ml for PCV13).<sup>232</sup> This assumption only affects the ELISA-based estimates shown below.

Table 15. PCV10 immunogenicity trial data, produced after the infant primary course

Serotypes	Vesikari et al, 1 month post 3 dose primary <sup>106</sup>				Silferdal et al, 1 month post primary <sup>108</sup>				Wysocki et al, 2 months post 2 dose primary <sup>105</sup>			
	% ELISA ≥ 0.20 µg/ml		% OPA titre ≥ 8		% ELISA ≥ 0.20 µg/ml		% OPA titre ≥ 8		% ELISA ≥ 0.20 µg/ml		% OPA titre ≥ 8	
	PCV10	PCV7	PCV10	PCV7	PCV10, 3 doses	PCV10, 2 doses	PCV10, 3 doses	PCV10, 2 doses	PCV10	PCV7	PCV10	PCV7
<b>4</b>	97.1	100	99.6	100	99.3	98	99.2	100	98.7	99.3	97.8	95.6
<b>6B</b>	65.9	79	92.4	95.5	63.1	55.7	88.9	74.4	64.1	30.8	63	35.2
<b>9V</b>	98.1	99.5	100	100	99.3	93.4	100	100	96.1	96.6	98.5	99.3
<b>14</b>	99.5	99.5	99.6	98.9	100	96.1	100	98.5	99.4	97.9	97.1	93.3
<b>18C</b>	96	98.9	93.6	95.5	99.3	96.1	96.2	82.8	87.8	97.3	59.8	77
<b>19F</b>	95.4	99.2	87.7	92.1	96.1	92.8	93.8	87	96.2	99.3	84.3	67.9
<b>23F</b>	81.4	94.1	93.9	97.7	77.6	69.3	97.7	86.3	75	74.7	97.1	87.8
<b>1</b>	97.3	4	65.7	4.5	98.7	97.4	62.9	60.8	95.8	4.2	48.8	0
<b>5</b>	99	1.9	90.9	3.4	100	96.1	90.8	82.6	96.5	2.1	74.6	0
<b>7F</b>	99.5	4.5	99.6	18.2	99.3	96.7	98.5	90.6	98.6	6.4	96.8	0
<b>6A</b>	22.2	31.2	58	68.5	NA	NA	NA	NA	33.1	4.3	60.5	26.8
<b>19A</b>	22.6	28.7	19.6	3.4	NA	NA	NA	NA	26.6	12.8	4.3	0

NA: not available

**Table 16. PCV10 input data scaled to serotype-specific vaccine efficacy(%) based on US case-control study, and adjusted for polysorbate 80 based on trial 009 and inconsistencies in 2 priming versus 3 priming dose responses**

Serotypes	Vesikari et al, 3 priming doses <sup>106</sup>		Wysocki et al, 2 priming doses <sup>105</sup>		Wysocki estimates replaced by Vesikari if worse point estimate	
	ELISA-based	OPA-based <sup>a</sup>	ELISA-based	OPA-based	ELISA-based, 2 doses	OPA-based, 2 doses <sup>a</sup>
<b>4</b>	90.3	92.6	92.4	95.1	90.3	92.6
<b>6B</b>	78.4	90.9	100.0	100.0	78.4	90.9
<b>9V</b>	98.6	100.0	99.5	99.2	98.6	99.2
<b>14</b>	94.0	94.7	95.4	97.8	94.0	94.7
<b>18C</b>	94.2	95.1	87.5	75.3	87.5	75.3
<b>19F</b>	83.7	82.8	84.3	100.0	83.7	82.8
<b>23F</b>	84.8	94.2	98.4	100.0	84.8	94.2
<b>1</b>	93.3	61.2	91.6	48.8	91.6	48.8
<b>5</b>	97.1	87.5	94.4	74.6	94.4	74.6
<b>7F</b>	95.0	81.4	92.2	96.8	92.2	81.4
<b>6A</b>	54.1	64.4	100.0	100.0	54.1	64.4
<b>19A</b>	22.6	19.6	26.6	4.3	22.6	4.3

<sup>a</sup> Selected for use in most analyses, as shown in the first subsection of the results

Table 17. PCV13 immunogenicity trial data, produced after the infant primary course

Serotypes	Kieninger et al, 3 priming doses <sup>153</sup>				Gadzinowski et al, 3 priming doses <sup>150</sup>		Snape et al, 2 priming doses <sup>151</sup>			
	% ELISA ≥ 0.35 µg/ml		% OPA titre ≥ 8		% ELISA ≥ 0.35 µg/ml	% OPA titre ≥ 8	% ELISA ≥ 0.35 µg/ml		% OPA titre ≥ 8	
	PCV13	PCV7	PCV13	PCV7	PCV13 <sup>a</sup>	PCV13 <sup>a</sup>	PCV13	PCV7	PCV13	PCV7
<b>4</b>	98.2	98.2	100	100	97.7	100	95.3	97	100	100
<b>6B</b>	77.5	87.1	96	98.9	77.3	96.9	40.2	50.5	89	75
<b>9V</b>	98.6	96.4	100	100	98.4	100	85.6	91.2	100	100
<b>14</b>	98.9	97.5	100	100	92.9	100	92.5	96.1	100	100
<b>18C</b>	97.2	98.6	100	98.9	96.1	100	92.8	87.3	97	98
<b>19F</b>	95.8	96	96	93.6	98.4	99	93.6	93.1	87	86
<b>23F</b>	88.7	89.5	96	95.7	82.8	100	66.7	65.7	96	97
<b>1</b>	96.1	1.4	93	4.3	93	84.2	97.2	0	89	1
<b>3</b>	98.2	6.3	99	24.5	93.7	98	86	2	100	20
<b>5</b>	93	31.6	99	4.3	90.6	89.2	89.3	17.5	92	0
<b>6A</b>	91.9	31.6	96	72	85.2	99	94.4	12	97	40
<b>7F</b>	98.6	4	94.9	7.4	100	95.8	79.2	2	100	57
<b>19A</b>	99.3	79.2	100	17	99.2	95.9	92.7	88.9	92	19

<sup>a</sup> PCV13 formulated with polysorbate 80, as the licensed vaccine. Other trialled vaccine formulations without polysorbate 80



Table 18. PCV13 immunogenicity input data scaled to serotype-specific vaccine efficacy (%) based on US case-control study

Serotypes	Whitney et al <sup>15</sup>	Kieninger et al, 3 priming doses <sup>153</sup>		Gadzinowski et al, 3 priming doses <sup>150</sup>		Snape et al, 2 priming doses <sup>151</sup>	
	PCV7/CDC	Elisa-based	OPA-based	Elisa-based	OPA-based	Elisa-based	OPA-based
<b>4</b>	93.0	93.0	93.0	92.5	93.0	91.4	93.0
<b>6B</b>	94.0	83.6	91.2	83.4	92.1	74.8	100.0
<b>9V</b>	100.0	100.0	100.0	100.0	100.0	93.9	100.0
<b>14</b>	94.0	95.3	94.0	89.6	94.0	90.5	94.0
<b>18C</b>	97.0	95.6	98.1	94.5	98.1	100.0	96.0
<b>19F</b>	87.0	86.8	89.2	89.2	92.0	87.5	88.0
<b>23F</b>	98.0	97.1	98.3	90.7	100.0	99.5	97.0
<b>1</b>	-	94.7	88.7	91.6	79.9	97.2	88.0
<b>3</b>	-	91.9	74.5	87.4	73.5	84.0	80.0
<b>5</b>	-	61.4	94.7	59.0	84.9	71.8	92.0
<b>6A</b>	76.0	100.0	100.0	100.0	100.0	100.0	100.0
<b>7F</b>	-	94.6	87.5	96.0	88.4	77.2	71.4
<b>19A</b>	26.0	99.3	100.0	99.2	95.9	92.7	92.0

**Table 19. PCV13 input data scaled to serotype-specific vaccine efficacy (%) based on US case-control study, and adjusted for polysorbate 80 and inconsistencies in 2 priming versus 3 priming dose point estimate responses**

Serotypes	Trial 009, European Medicines Agency, 3 priming doses			Kieninger et al, adjusted for polysorbate 80, 3 priming doses <sup>153</sup>		Snape et al, adjusted for polysorbate 80, 2 priming doses <sup>151</sup>		Snape replaced by Kieninger if worse point estimate, 2 priming doses	
	ELISA, 3+1 +P80	ELISA, 3+1-P80	Ratio	ELISA-based	OPA-based <sup>a</sup>	ELISA-based	OPA-based	ELISA-based	OPA-based <sup>a</sup>
<b>4</b>	93.3	94.1	0.99	92.2	93.0	90.6	93.0	90.6	93.0
<b>6B</b>	60.9	66.4	0.92	76.7	91.2	68.6	100.0	68.6	91.2
<b>9V</b>	97.1	97.5	1.00	99.6	100.0	93.5	100.0	93.5	100.0
<b>14</b>	94.5	97.5	0.97	92.4	94.0	87.7	94.0	87.7	94.0
<b>18C</b>	97.9	97.9	1.00	95.6	98.1	100.0	96.0	95.6	96.0
<b>19F</b>	95.8	98.3	0.97	84.6	89.2	85.2	90.8	84.6	89.2
<b>23F</b>	86.1	92.4	0.93	90.5	98.3	92.7	98.7	90.5	98.3
<b>1</b>	95.8	92.4	1.04	98.2	80.3	100.0	79.3	98.2	79.3
<b>3</b>	97.9	99.2	0.99	90.7	73.7	82.9	78.9	82.9	73.7
<b>5</b>	94.1	92.4	1.02	62.5	85.3	73.1	82.5	62.5	82.5
<b>6A</b>	86.6	86.1	1.01	100.0	100.0	100.0	100.0	100.0	100.0
<b>7F</b>	98.7	99.6	0.99	93.7	88.3	76.5	72.1	76.5	72.1
<b>19A</b>	98.7	100	0.99	98.0	95.9	91.5	88.2	91.5	88.2

<sup>a</sup> Selected for use in most analyses, as shown in the first subsection of the results

### 8.2.2.2 Vaccine efficacy estimates against AOM and pneumonia

Since we have only incidence data on all cause otitis media and pneumonia consultations and hospitalisations, we apply the more general estimates from the trials as discussed in the review sections above. We use the median of three estimates produced by De Wals et al<sup>132</sup> for estimated incremental efficacy versus hat PCV7. In De Wals et al<sup>132</sup> a specific in-depth analysis is presented on estimating AOM efficacy based on the trial data. Basically, De Wals et al<sup>132</sup> adjusted clinical trial results on AOM with the prevalence of otopathogens based on three data sets (1 from a multinational survey<sup>233</sup>, 1 from the control group in the FinOM trial<sup>234</sup>; 1 from the control group of the POET trial<sup>8</sup>. Assuming no serotype replacement occurred in these trials, they found incremental efficacy for PCV13 versus PCV7 of 0.5%, 1.1% and 2.8%, for PCV10 (including NTHI) versus PCV7 of 10.3%, 11.2% and 11.2%, for PCV10 (excluding NTHI) versus PCV7 of 4.3%, 3.1% and 5.2%, respectively. De Wals et al<sup>132</sup> explained the lower results for PCV13 based on a higher level of replacement that occurred in the PCV7 trials (on which, in the absence of clinical data on PCV13, the estimates for PCV13 are based) than in the PCV11 trial (the basis for the clinical efficacy of PCV10 versus AOM). Since any assumptions we make on AOM differences between PCV10 and PCV13 will be influential on the results and potentially disputable, we do not only use the results based on De Wals et al<sup>132</sup>, but we also show all results with and without including an impact on NTHI, and present results with a large number of additional estimates for the incremental efficacy on all-cause AOM these vaccines may have over each other. For pneumonia, we also use data available to date for both vaccines. That is, for PCV13 based on pivotal trial data for PCV7<sup>235</sup>, and for PCV10 trial data which have become available from a trial conducted in Latin America.<sup>134 135</sup> Vaccine efficacy for pneumonia (see table 20) is adjusted in the model based on the pre-PCV7 serotype distribution (as reported in the previous report<sup>4</sup>), the latest available (2009) serotype distribution and the PCV10 and PCV13 serotype coverage distributions, respectively, to account for the fact that the clinical trial results on pneumonia available today are based on observations in countries without PCV7 vaccination, and without PCV7 in the control arm. This brings the difference between the pneumonia estimates between the two vaccines closer together.

**Table 20. Vaccine efficacy estimates used as input in the model**

Vaccine efficacy estimates	Mean vaccine efficacy	Estimated distribution	Source
<b>PCV serotypes</b>			
1 dose < 7 months	73%	LogNormal(0.112)	Whitney et al <sup>15</sup>
2 or 3 doses < 7 months	96%	LogNormal(0.028)	
2+1 schedule	98%	Beta(3.7463, 0.076455)	
3+1 schedule	100%	LogNormal(0.015)	
<b>PCV10</b>			
Pneumonia (suspected CAP)	7.3%	LogNormal(0.028)	ESPID abstract, 2011 <sup>134 135</sup> ; De Wals <sup>132</sup> , based on Eskola <sup>234</sup> ; Prymula <sup>8</sup> ; Jacobs <sup>233</sup>
Otitis media <sup>a</sup>	4.3%	Beta (64.5, 1435.5)	
Otitis media with NTHI <sup>a</sup>	11.2%	Beta (168, 1332)	
<b>PCV13</b>			
Pneumonia	6%	LogNormal (0.032)	Black <sup>235</sup> ; De Wals <sup>132</sup> based on Eskola <sup>234</sup> ; Prymula <sup>8</sup> ; Jacobs <sup>233</sup>
Otitis media <sup>a</sup>	1.1%	Beta (16.5, 1483.5)	

<sup>a</sup> Already adjusted as an incremental measure of efficacy versus PCV7

### 8.2.2.3 Vaccine efficacy estimates: further assumptions and adjustments

The resulting efficacy estimates for IPD by serotype as well as for pneumonia and otitis media are further adjusted in the model for each type of schedule, again based on the US case-control study (see table 1), and according to vaccine uptake for each dose (97%, 92%, 92% and 85% for doses at months 2, 3, 4 and 12, respectively). It is assumed that children vaccinated at later moments have also received their vaccines at previous vaccination moments.

We additionally apply a dose specific exponential waning function on all efficacy estimates, to account for the fact that infants receiving fewer doses will lose their (lower) protection earlier than infants having received more doses. Unless specified otherwise, efficacy wanes completely after the first dose from age 3 months to age 24 months, after the second dose at 3 months from age 5 months to age 36 months, after the second dose at age 4 months from age 6 months to 36 months, after the third dose at age 4 months from age 6 months to age 60 months, and after the booster dose at age 12 months from age 15 months to age 10 years. Therefore, all direct protective efficacy is assumed to have waned by age 10 years, unless specified otherwise. In view of the time spans we use to account for the occurrence of new cases (i.e. 5 and 10 years), the impact of these waning assumptions are expected to be small, but nonetheless we also show results without the impact of waning included.

For the purpose of probabilistic sensitivity analyses (PSA), vaccine efficacy point estimates have been assigned Lognormal distributions, based on their 95% Confidence Interval. In the absence of normality, the other IPD efficacy estimates have been assigned beta distributions by age and by dose where required.

The current lack of knowledge regarding the extent of expected serotype (and possibly pathogen) replacement ("STR" henceforth) can be expressed by assuming STR will occur according to a uniform distribution between 0% (no STR) and 99% (nearly complete STR) across all ages. STR is introduced in the model as a parameter that reduces the serotype coverage for IPD. This implies that a percentage change in STR is modeled to reduce the effectiveness of PCV13 to the same extent as the effectiveness of PCV10. In other words, the interpretation of serotype replacement in this model is vaccine-specific in that the same percentage change implies nonetheless that more serotype replacement is needed to occur for PCV13 than for PCV10, in order to have the same decrease in serotype coverage. For pneumonia and otitis media, STR is introduced directly as a reduction in vaccine efficacy. We apply STR to IPD, pneumonia and otitis media, and show the impact of alternative assumptions (e.g. no STR and various levels of STR on IPD only).

As discussed in the review sections above, herd immunity effects have been observed in the US following the introduction of PCV7. In separate analyses, we show the impact of assuming similar effects as observed in the US. In order to do this, we sample from progressive herd immunity impacts by age group and year reported by Ray et al<sup>200</sup> and the Active Bacterial Core surveillance (ABCs) United States, in the first 5 years of PCV7 use in the US, net of vaccine type replacement effects. Unless specified otherwise, these data are as shown in table 21.

**Table 21. Assumed herd immunity, expressed as a reduction in cases at each age**

Age group (years)	Mean	Distribution
<5	3%	Triangular (0, 0.025, 0.05)
5-15	45%	Triangular (0.207348, 0.483812, 0.656602)
15-45	60%	Triangular (0.348448, 0.64463, 0.818854)
45-65	12%	Triangular (0.033783, 0.168915, 0.168915)
65+	36%	Triangular (0.063373, 0.459458, 0.570361)

We apply herd immunity in the first place to IPD only, but explore the impact of extending these assumptions such that herd immunity is assumed for pneumonia and otitis media, proportional to IPD induced herd immunity. For pneumonia, estimating herd immunity requires an additional assumption of the proportion of all-cause pneumonia cases caused by pneumococcus. This was estimated as a uniform distribution between 20% and 40%, based on De Wals et al.<sup>196</sup> (citing<sup>236,237</sup>) and Melegaro et al.<sup>213</sup> For otitis media, a similar assumption was made: the proportion of otitis media cases caused by pneumococcus and NTHI were each assigned a uniform distribution between 20% and 32%. This assumption is based on data suggesting that 80% of AOM is caused by bacteria, of which 25% to 40% are pneumococcus, and 50% to 80% are either pneumococcus or NTHI.<sup>238</sup> Therefore, we assigned uniform distributions of 20% to 32% to the proportion of AOM due to pneumococcus and (in case of including vaccine effects on NTHI) of 40% to 64% to the proportion of AOM due to either pneumococcus or NTHI.

### 8.2.3 Direct costs

To gain insight in costs that are attributable to pneumococcal infections, in collaboration with the Christian Mutualities (CM), we carried out an intensive national face-to-face survey. Surviving CM members with known pneumococcus isolation date (a total of 915) were contacted by telephone on a regional basis, and 146 face to face interviews were carried out (55 relating to children (average age 1.4 years), 91 to adults (average age 54 years)). The health care costs were based on actual expenditures of the CM sickness funds, which were identified as related to the patients' episode during the interview. A more detailed description of this survey and the questionnaires that were used are available from the previous PCV7 KCE report.<sup>4</sup>

The average direct costs are summarised in Table 22 per disease category. For direct health care costs of conditions with hospitalisation, the proportion of hospitalisation costs are given along with the rounded average length of stay in days (ALOS) in brackets.

The Belgian Consumer Price Indices for health care expenditures show slight deflation (i.e. CPI health care (2010) < CPI health care (2006), with a relative index of 2010 versus 2006 of 98.5%).<sup>b</sup> However, within the basket of health care expenditures, consultations and hospitalisation costs (which are likely to be prevented to a greater extent than their average weighting in the healthcare CPI reflects) tend to show an inflationary effect. For this reason, and because such a slight adaptation would have only a very minor impact on the comparison between options, we decided to maintain the price level at a par with the input cost data for the 2006 analysis.

The current public price for PCV7, PCV10 and PCV13 is €66.15, €70.44 and €74.55 per dose, respectively.<sup>c</sup> Although the tendered price is likely to be substantially different, we will use these price differences in the first set of analyses. Additionally, the expansion from a 2+1 schedule to a 3+1 schedule has been assumed to cost €5 per vaccinated child in administration and organisation costs (expert committee assumption).

<sup>b</sup> Source: FOD Economie, KMO, Middenstand en energie, <http://economie.fgov.be/nl/statistieken/cijfers/economie/consumptieprijzen/consumptieprijsindexen/> accessed 1<sup>st</sup> April 2011)

<sup>c</sup> source: Gecomentarieerd Geneesmiddelenrepertorium of the Belgisch Centrum voor Farmacotherapeutische Informatie, <http://www.bcfi.be/GGR/Index.cfm?ggrWelk=MAIN>, accessed 1<sup>st</sup> April 2011

**Table 22. Average direct costs for disease caused by pneumococcus among 146 patients (2006)**

	Direct health care costs (EURO)				Fitted distributions	
	National Health System (a)		Personal (b)			
	≤ 5 y	> 5 y	≤ 5 y	> 5 y	≤ 5 y	> 5 y
<b>Meningitis</b>	8,085 (78%, 15)*	7,980 (89%, 20)	1,267 (54%, 15)	680 (78%, 20)	Loglogistic	Gamma
<b>Bacteremia/ Septicaemia</b>	2,383 (96%, 9)	6,903 (91%, 20)	352 (90%, 9)	685 (75%, 20)	Weibull	Weibull
<b>Hospitalised pneumonia</b>	3,712 (86%, 9)	5,365 (89%, 16)	879 (56%, 9)	899 (75%, 16)	Gamma	Loglogistic
<b>Non-hospitalised pneumonia</b>	713	713	304	304	NA	NA
<b>Non hospitalised AOM without complications</b>	58	58	22	22	NA	NA
<b>Non hospitalised AOM with complications</b>	501	79	353	51	LogNormal	NA
<b>AOM hospitalised</b>	3,072 (78%, 3)	3,426 (86%, 9)	625 (50%, 3)	383 (65%, 9)	Loglogistic	NA
<b>Other</b>	3,204 (97%, 7)	2,299 (88%, 8)	256 (84%, 7)	355 (79%, 8)	NA	NA

\* For hospitalised cases the proportion of direct health care cost incurred in hospital is given in brackets along with the rounded average length of stay.

(a) Direct health care costs for RIZIV/INAMI. These costs arose for the following categories: GP consultations, specialist consultations (paediatrics, internal medicine, neurology, ortolaringo, other), physiotherapy, logopedist, other health care professions, technical procedures (blood tests, X-rays), medication (mainly antibiotics and painkillers), care products (ointments, disinfectants), Technical physical aids (prothese, hearing aid, wheel chair), nursing (home care).

(b) Direct health care costs paid by patients and their family. The same categories as under (a) gave rise to these costs.

In the baseline analysis direct health care costs arising to both the health care system and individuals are considered under the health care payer's perspective. These direct costs were directly quantifiable from the CM records.

To reflect variability in the data, distributions were fitted to the individual cost data. Goodness of fit and subsequent selection of cost distributions was based on both the Anderson-Darling and Kolmogorov-Smirnov Statistics. As indicated in table 22, all these cost distributions are skewed (long-tailed). In view of the importance of the age-specific contribution of hospitalisation costs in the direct health care costs, the distributions fitted to the costs for hospitalised conditions were adjusted based on the average length of stay of these conditions by age.

Direct non-health care costs are ignored in the analysis. It could be argued that part of these direct costs are implicitly included in the QALY loss estimates (see below), and these costs are relatively rare and therefore likely less representative in this survey. Similar problems arise when trying to estimate the future costs of long term care, on the basis of the survey. Therefore, in addition to the short term direct health care costs (based on records and interviews), direct costs of long term sequelae are considered in addition to the estimates in table 22.

Long term costs of sequelae, not fully captured in the survey, were based on two previous KCE reports.<sup>239 240</sup> Beguin et al<sup>239</sup> write that INAMI-RIZIV reimburses approximately €500 for any type of hearing aid while the retail price is in the range of approximately €500 to €2475.<sup>239</sup> Based on their distribution of sales over various price classes, we estimated the costs of hearing aid replacement to the health care payer at €1800.

The costs of sequelae from impaired hearing were thus estimated over the remaining (age-specific) lifetime for persons incurring severe hearing deficit, using a replacement frequency of once every 3 years in children and once every 5 years in adults (>18 years).<sup>239</sup> The costs of long term care for severe neurological sequelae (due to meningitis) were estimated at €40,000 per year based on data presented in a study on long term care for persons with acquired brain injury.<sup>240</sup> Note that these estimates are internationally in line with earlier publications.<sup>159</sup>

#### 8.2.4 Health-Related Quality of Life

Estimates from the literature are used for quality of life weights. Unless stated otherwise, like most economic evaluations on PCV7, PCV10 or PCV13 we apply the estimates summarised by Melegaro et al.<sup>228</sup> Additionally in sensitivity analysis, the estimates by Salo et al.<sup>241</sup> (some of which overlap with those of Melegaro et al.<sup>228</sup>) are applied. The estimated QALY losses for these two sets of QALY estimates are given in table 23. Note that a study for pneumococcal disease in children in the USA<sup>205</sup> found values which were orders of magnitude greater than reported in the studies in table 23, but was criticised for methodological shortcomings.<sup>206</sup>

**Table 23: Losses in Health-related Quality-Adjusted Life-Years (QALYs) for health states related to pneumococcal disease**

	Melegaro et al. <sup>228</sup>	Salo et al. <sup>241</sup>
<b>Bacteremia</b>	0.0079 per case	0.006 per case
<b>Meningitis</b>	14% severe bilateral hearing loss at 0.460 QALY loss per case in the first year + 0.2 QALY loss every later year	31% any deafness at 0.216 QALY loss per case in the first year + 0.054 QALY loss every later year
<b>Pneumonia outpatient</b>	0.004 per case	0.004 per case
<b>Pneumonia inpatient</b>	0.006 per case	0.006 per case
<b>AOM</b>	0.005 per episode	0.005 per episode

An alternative way of constructing a combined measure of morbidity and mortality is to use DALYs. As an additional form of uncertainty analysis, the results are also shown in the form of costs per DALYs averted, based on Australian estimates of DALY weights as reported in Butler et al.<sup>242</sup>

The estimates of utility losses for AOM are of particular interest since there are important differences in effectiveness between PCV10 and PCV13 in relation to AOM. It is noteworthy that the 0.005 QALY decrement per episode, used by all cost-utility analyses (except those by Lieu et al.<sup>202</sup> and O'Brien et al.<sup>192</sup>, who use the higher estimates from Prosser et al.<sup>205</sup> (0.011 per episode)) stems from a 1996 study by Oh et al.<sup>243</sup> A more recent trial by Petrou et al.<sup>244</sup> found great divergence in the estimated utility weight derived by the Health Utilities Index 2, Health Utilities Index 3 or EQ-5D, which resulted in estimated QALY losses (for otitis media with effusion in the placebo group) of 0.028, 0.053 and 0.004, respectively. The EQ-5D estimate is best in accordance with those presented by Oh et al.<sup>243</sup>, and is the recommended instrument for economic evaluations in Belgium.<sup>223</sup>

## 8.3 RESULTS

As explained above, there are considerable differences in interpretation of the efficacy estimates produced by RCTs relevant to PCV10 and PCV13. In this section we first present cost-effectiveness acceptability curves (CEACs), which exhibit the parameterisable uncertainty of the options for vaccination. These are based on 1000 model iterations for each scenario (using Latin Hypercube sampling), assuming there is no herd immunity. The CEACs in figures 15 to 17 show the proportion of simulations that are below a given cost-effectiveness ratio, and as such it can be related to a willingness to pay of societal policy makers to gain QALYs in their population.

### 8.3.1 Cost-effectiveness acceptability curves

Inspection of figures 15 through 17 allows to make some general inferences:

- Using a pragmatic (unofficial) willingness to pay threshold of €30,000 per QALY gained, both PCV10 and PCV13 are likely to be judged cost-effective when compared to the current situation. The 3+1 schedule is less likely to be cost-effective than the 2+1 schedule, and at the current price level PCV13 is less likely to be cost-effective than PCV10. These observations may be largely explained by the fact that we use in this part of the analysis the current public (pharmacy) prices (which implies between PCV13 and PCV10 a €4.11 price difference per dose) and assume additional administration costs of €5 per child are required with the addition of an extra dose to the infant vaccination schedule (3+1 schedule only).
- The CEACs produced by the different methods for IPD effectiveness are comparable in shape and probability distribution. Furthermore, among the methods informed the most by data (the ELISA and OPA methods), there appears to be no decision changing influence from choosing one method over another one. For PCV10 the least attractive approach is to use the average method, excluding any cross protection on serotype 19A, which is regarded as an emerging serotype in Belgium and other European countries. The OPA-based estimates (which assume implicitly that the percentage of vaccines with OPA response >8 is a good correlate of clinical protection) tend towards the centre of the various estimates. For PCV13 the least attractive approach is to use the OPA method, but the differences obtained with the different effectiveness methods are much smaller, implying that PCV13 has a relatively consistent efficacy, over the various approaches to evaluate it.
- For PCV10, the differences obtained by the different effectiveness methods are heavily influenced by whether or not the effectiveness of PCV10 against NTHI is included in the analysis.
- As can be expected, the Incremental Cost-Effectiveness Ratios (ICERs) tend to be lower with herd immunity effects included (since relatively more benefits are allowed to accrue to vaccination), and hence the CEACs have a relatively higher and more leftward position, but the differences between the different effectiveness methods remains similar or smaller (the latter implying that the impact of indirect effects quickly dominates that of direct effects).

In view of the previous points and in order to allow for a manageable output and analysis of other aspects of the decision problems discussed in this report, we will use in what follows (unless specified otherwise) only the OPA based effectiveness estimates, but explore further the impact of assumptions on PCV10's effectiveness against NTHI AOM, PCV10 and PCV13's impact on all cause AOM and pneumonia, and the influence of serotype replacement and herd immunity.



Figure 15. Cost-effectiveness acceptability curves (€) for PCV10 (3+1 schedule) versus current situation (PCV7, 2+1 schedule), current public vaccine prices and a time span of 5 years, upper panel: no herd immunity, lower panel: with herd immunity

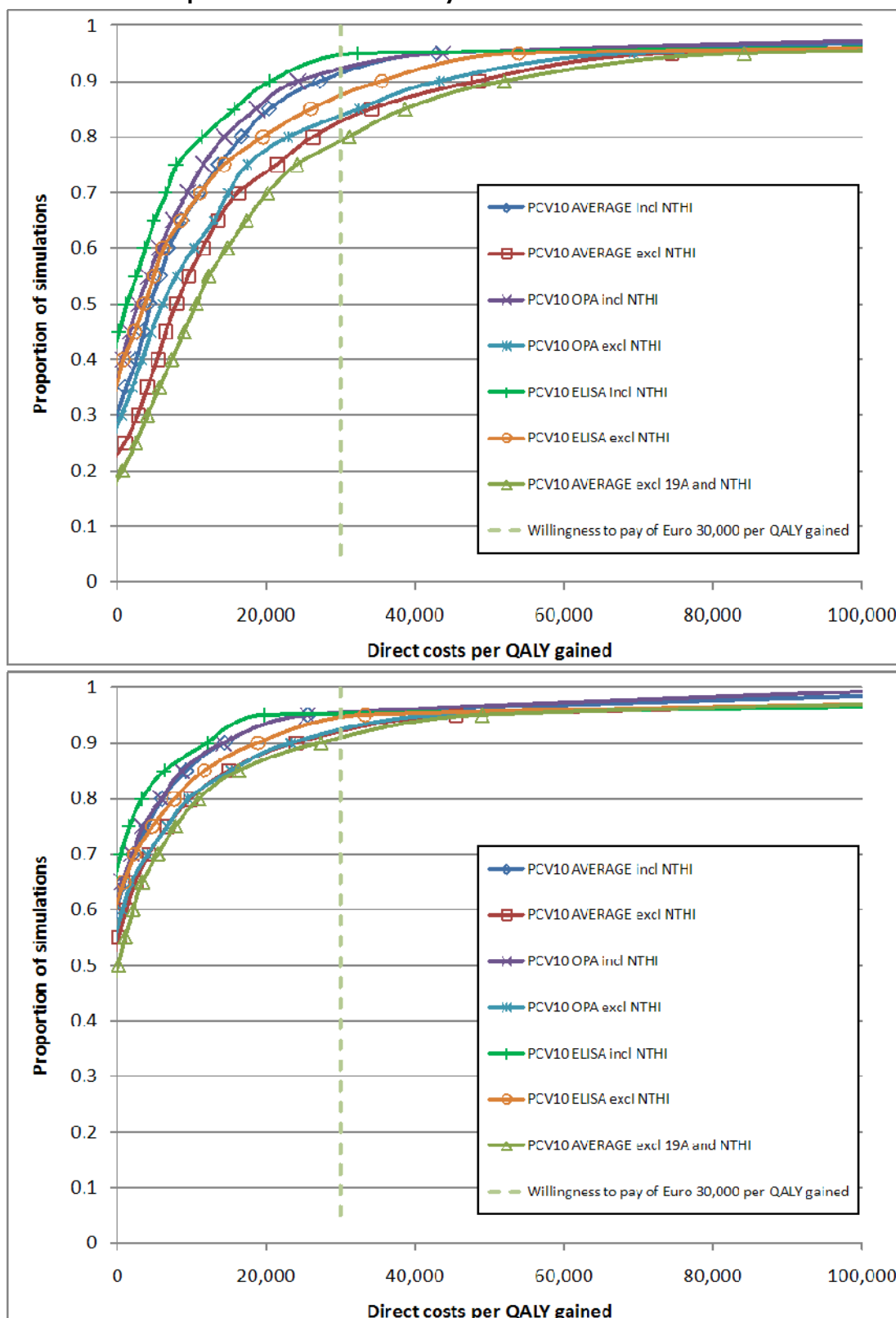


Figure 16. Cost-effectiveness acceptability curves (€) for PCV13 (2+1 schedule) versus current situation (PCV7, 2+1 schedule), current public vaccine prices and a time span of 5 years, upper panel: no herd immunity, lower panel: with herd immunity

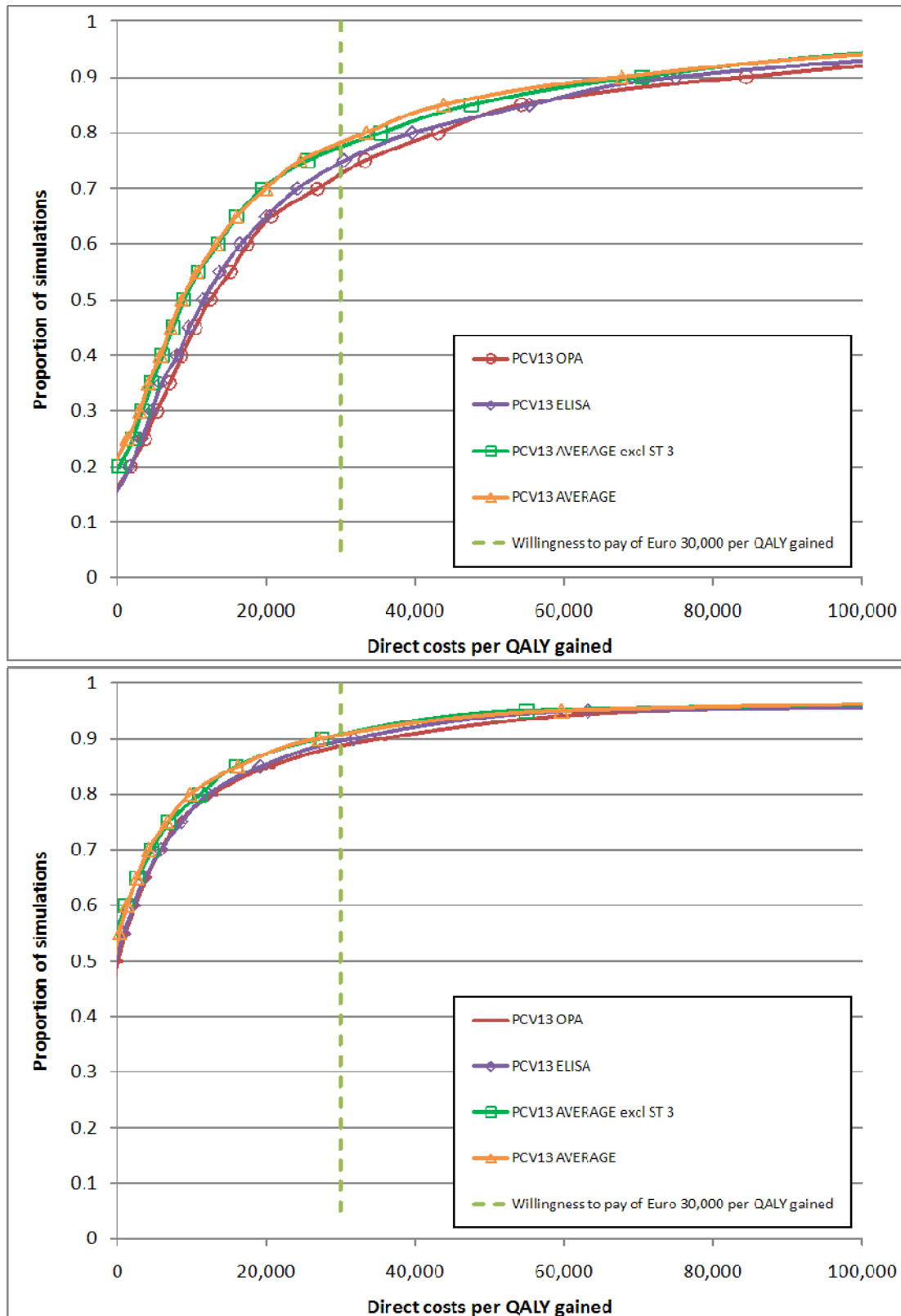
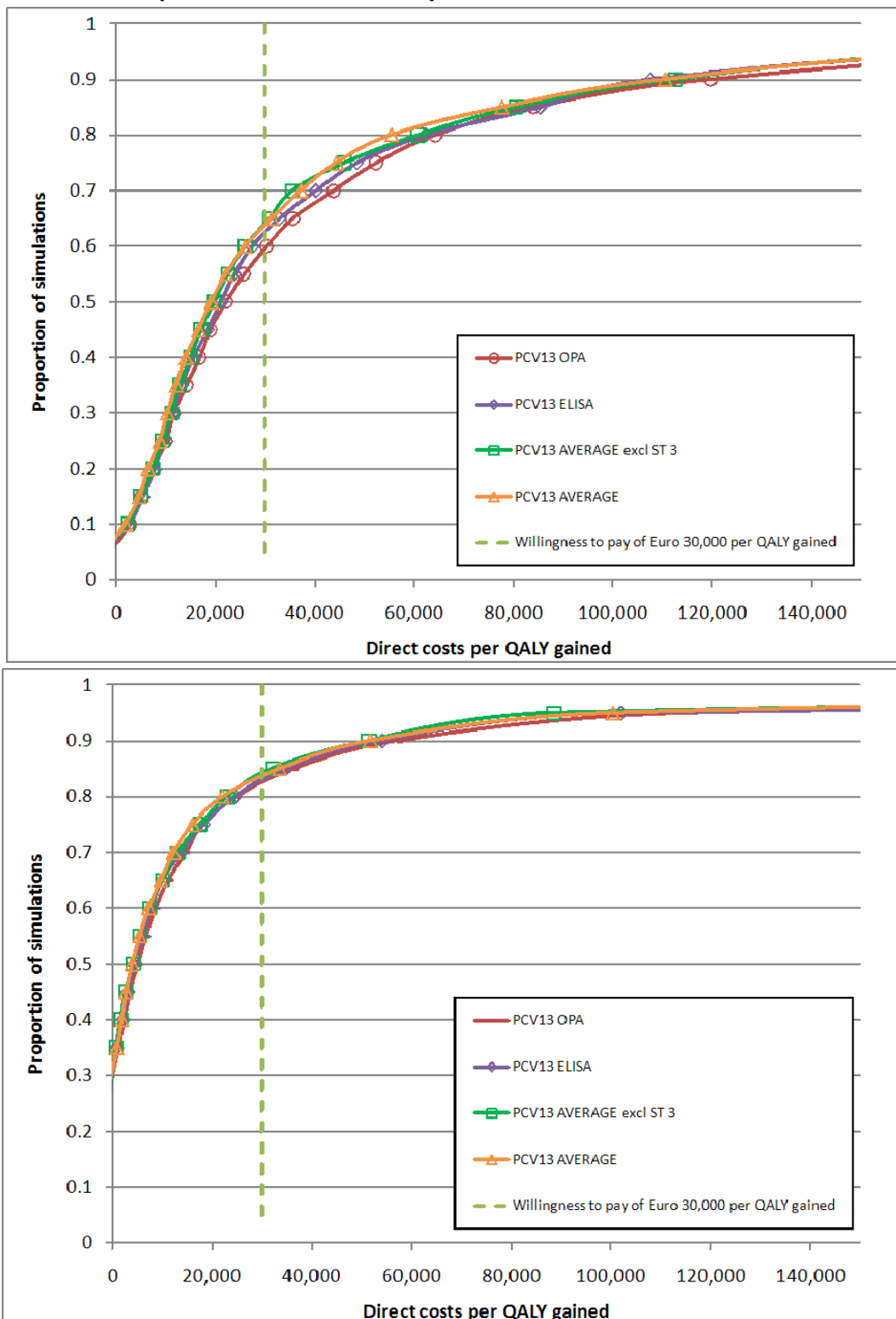


Figure 17. Cost-effectiveness acceptability curves (€) for PCV13 (3+1 schedule) versus current situation (PCV7, 2+1 schedule), current public vaccine prices and a time span of 5 years, upper panel: no herd immunity, lower panel: with herd immunity



### 8.3.2 Incremental costs, outcomes and cost-effectiveness ratios

Tables 22 to 26 below show the projected costs and effects in more detail and confirm that the ICERs of PCV10 and PCV13 for both the 2+1 and 3+1 schedules versus the current situation are within previously acceptable ranges, at current vaccine prices, even when serotype replacement is assumed to be uniformly distributed between 0% and 99%. Note that herd immunity effects improve the ICERs, but are not required to obtain attractive ICERs for both new vaccine formulations. The incremental cost-effectiveness of the 3+1 schedule versus the 2+1 schedule is high and uncertain (with the 3+1 schedule being dominated (i.e. less effective, more costly) by the 2+1 schedule in 10.8% of simulations) and therefore the 3+1 schedule is highly unlikely to be judged a worthwhile option. Note that we assume that both schedules would yield the same herd immunity effects. If the 3+1 schedules would yield substantially more herd immunity or provoke less STR, then it could lower the ICER of the 3+1 versus the 2+1 schedule to a level where it may become acceptable. However, at present, the evidence from post-PCV7 observational studies suggests there is no differential impact of a reduced schedule on either of these indirect aspects.

**Table 22. Estimated median costs and effects (and 95% interval) of pneumococcal conjugate vaccination with PCV10 or PCV13 in a 2+1 schedule versus the current situation (PCV7 in a 2+1 schedule), using current public pharmacy vaccine prices, a 5 year time span for infections to accrue, a wide ranging uniform distribution of serotype replacement, and excluding herd immunity effects (results of 1000 model iterations)**

	Median			5 <sup>th</sup> percentile			95 <sup>th</sup> percentile		
	PCV10 incl NTHI	PCV10 excl NTHI	PCV13	PCV10 incl NTHI	PCV10 excl NTHI	PCV13	PCV10 incl NTHI	PCV10 excl NTHI	PCV13
<b>Cases prevented</b>									
IPD	101	101	113	12	12	13	198	196	220
Pneumonia	195	192	181	26	24	21	540	538	594
Otitis media	5,937	2,241	546	703	276	66	11,571	4,473	1,217
Deaths	1.59	1.57	1.66	0.19	0.18	0.21	4.20	4.13	4.72
<b>Direct costs prevented</b>									
<b>Health care</b>	<b>€ 1,797,165</b>	<b>€ 1,444,555</b>	<b>€ 1,389,291</b>	<b>€ 575,744</b>	<b>€ 404,102</b>	<b>€ 320,560</b>	<b>€ 4,393,578</b>	<b>€ 3,881,686</b>	<b>€ 3,981,570</b>
Meningitis	€ 652,497	€ 636,206	€ 660,781	€ 63,013	€ 65,681	€ 77,173	€ 2,365,078	€ 2,338,457	€ 2,494,273
Bacteremia	€ 70,152	€ 70,194	€ 74,065	€ 6,425	€ 6,992	€ 6,337	€ 260,966	€ 239,689	€ 283,577
Other IPD	€ 88,263	€ 91,759	€ 106,703	€ 9,167	€ 8,473	€ 8,863	€ 427,811	€ 404,817	€ 513,656
Pneumonia	€ 196,448	€ 193,369	€ 216,151	€ 13,693	€ 12,648	€ 9,282	€ 1,667,052	€ 1,602,533	€ 1,702,908
Otitis media	€ 466,804	€ 176,830	€ 43,123	€ 55,129	€ 22,291	€ 5,729	€ 941,486	€ 377,788	€ 104,147
<b>Vaccination</b>	<b>-€ 1,416,906</b>	<b>-€ 1,416,906</b>	<b>-€ 2,774,361</b>	<b>-€ 1,416,906</b>	<b>-€ 1,416,906</b>	<b>-€ 2,774,361</b>	<b>-€ 1,416,906</b>	<b>-€ 1,416,906</b>	<b>-€ 2,774,361</b>
<b>Total</b>	<b>€ 380,259</b>	<b>€ 27,649</b>	<b>-€ 1,385,071</b>	<b>-€ 841,161</b>	<b>-€ 1,012,804</b>	<b>-€ 2,453,802</b>	<b>€ 2,976,672</b>	<b>€ 2,464,780</b>	<b>€ 1,207,209</b>
<b>Quality-adjusted life-years gained</b>									
<b>Total</b>	<b>123.08</b>	<b>102.22</b>	<b>100.31</b>	<b>34.97</b>	<b>23.41</b>	<b>15.65</b>	<b>261.59</b>	<b>236.40</b>	<b>253.06</b>
IPD	89.11	89.69	95.61	10.49	10.68	11.41	224.72	221.04	248.80
Pneumonia	1.31	1.29	1.26	0.17	0.17	0.12	4.88	4.75	5.52
Otitis media	29.21	10.98	2.66	3.45	1.30	0.35	60.24	24.21	6.34
<b>Incremental Cost-Effectiveness Ratios (ICERs): Incremental direct costs per...</b>									
Life-year gained	DOMINANT	DOMINANT	€ 15,337	DOMINANT	DOMINANT	DOMINANT	€ 61,453	€ 88,032	€ 218,603
QALY gained	DOMINANT	DOMINANT	€ 12,438	DOMINANT	DOMINANT	DOMINANT	€ 20,383	€ 37,295	€ 142,158
DALY averted	DOMINANT	DOMINANT	€ 11,114	DOMINANT	DOMINANT	DOMINANT	€ 28,878	€ 46,367	€ 131,008

Dominant: direct cost-savings versus the comparator, and at the same time gaining health outcomes versus the comparator. Each row shows at the second and third main column heading, the 5<sup>th</sup> and 95<sup>th</sup> percentile of the variable distribution in that row, respectively. That is the values are given at each row from low to high. Since the distributions of costs and effects are correlated, comparisons between rows are not always straightforward (e.g., the row total costs prevented (direct health care costs, net of vaccination costs) is shown from low (worst) to high (best), whereas the ICERs are in their row also shown from low (best) to high (worst)).

**Table 23. Estimated median costs and effects (and 95% interval) of pneumococcal conjugate vaccination with PCV10 or PCV13 in a 3+1 schedule versus the current situation (PCV7 in a 2+1 schedule), using current public pharmacy vaccine prices, a 5 year time span for infections to accrue, a wide ranging uniform distribution of serotype replacement, and excluding herd immunity effects (results of 1000 model iterations)**

	Median			5 <sup>th</sup> percentile			95 <sup>th</sup> percentile		
	PCV10 incl NTHI	PCV10 excl NTHI	PCV13	PCV10 incl NTHI	PCV10 excl NTHI	PCV13	PCV10 incl NTHI	PCV10 excl NTHI	PCV13
<b>Cases prevented</b>									
IPD	116	118	130	14	13	15	223	224	248
Pneumonia	232	236	209	30	29	23	676	624	678
Otitis media	6317	2373	587	764	292	71	12300	4773	1310
Deaths	1.7	1.7	1.9	0.2	0.2	0.2	4.8	4.5	5.3
<b>Direct costs prevented</b>									
Health care	€ 2,012,744	€ 1,644,628	€ 1,548,047	€ 646,149	€ 443,215	€ 341,853	€ 4,829,734	€ 4,399,429	€ 4,505,196
Meningitis	€ 708,202	€ 695,112	€ 721,167	€ 67,840	€ 71,008	€ 80,715	€ 2,595,001	€ 2,531,018	€ 2,844,385
Bacteremia	€ 78,866	€ 79,847	€ 82,130	€ 7,136	€ 7,405	€ 6,636	€ 289,855	€ 268,621	€ 316,379
Other IPD	€ 105,400	€ 107,111	€ 121,795	€ 10,519	€ 10,126	€ 9,976	€ 510,596	€ 483,505	€ 578,247
Pneumonia	€ 234,152	€ 237,378	€ 235,822	€ 14,693	€ 14,522	€ 9,948	€ 1,920,880	€ 1,964,777	€ 1,989,925
Otitis media	€ 499,199	€ 188,119	€ 46,190	€ 59,370	€ 23,544	€ 6,387	€ 994,817	€ 399,032	€ 110,813
Vaccination	-€ 2,444,128	-€2,444,128	-€4,257,372	-€2,444,128	-€2,444,128	-€4,257,372	-€ 2,444,128	-€ 2,444,128	-€ 4,257,372
<b>Total</b>	<b>-€ 431,384</b>	<b>-€ 799,500</b>	<b>-€2,709,324</b>	<b>-€1,797,979</b>	<b>-€2,000,913</b>	<b>-€3,915,519</b>	<b>€ 2,385,605</b>	<b>€ 1,955,300</b>	<b>€ 247,824</b>
<b>Quality-adjusted life-years gained</b>									
<b>Total</b>	<b>133.10</b>	<b>111.42</b>	<b>112.85</b>	<b>36.61</b>	<b>24.81</b>	<b>16.99</b>	<b>288.19</b>	<b>258.83</b>	<b>290.54</b>
IPD	99.20	97.44	108.16	11.30	11.40	12.58	252.68	243.68	284.72
Pneumonia	1.55	1.56	1.46	0.18	0.19	0.13	5.72	5.69	6.18
Otitis media	31.49	11.70	2.86	3.64	1.42	0.37	64.56	25.64	6.81
<b>Incremental Cost-Effectiveness Ratios (ICERs): Incremental direct costs per...</b>									
Life-year gained	€ 4,320	€ 8,337	€ 28,181	DOMINANT	DOMINANT	DOMINANT	€ 156,886	€ 181,480	€ 351,260
QALY gained	€ 2,876	€ 6,127	€ 22,057	DOMINANT	DOMINANT	DOMINANT	€ 43,671	€ 69,331	€ 212,364
DALY averted	€ 2,948	€ 5,745	€ 19,180	DOMINANT	DOMINANT	DOMINANT	€ 62,787	€ 84,323	€ 200,380

Dominant: direct cost-savings versus the comparator, and at the same time gaining health outcomes versus the comparator. Each row shows at the second and third main column heading, the 5<sup>th</sup> and 95<sup>th</sup> percentile of the variable distribution in that row, respectively. That is the values are given at each row from low to high. Since the distributions of costs and effects are correlated, comparisons between rows are not always straightforward (e.g., the row total costs prevented (direct health care costs, net of vaccination costs) is shown from low (worst) to high (best), whereas the ICERs are in their row also shown from low (best) to high (worst)).

**Table 24. Estimated median costs and effects (and 95% interval) of pneumococcal conjugate vaccination with PCV10 or PCV13 in a 3+1 schedule versus the same vaccine in a 2+1 schedule, using current public pharmacy vaccine prices, a 5 year time span for infections to accrue, a wide ranging uniform distribution of serotype replacement, and assuming no or equal herd immunity effects (results of 1000 model iterations)**

	Median			5 <sup>th</sup> percentile			95 <sup>th</sup> percentile		
	PCV10 incl NTHI	PCV10 excl NTHI	PCV13	PCV10 incl NTHI	PCV10 excl NTHI	PCV13	PCV10 incl NTHI	PCV10 excl NTHI	PCV13
<b>Cases prevented</b>									
IPD	13.19	11.92	12.61	-0.65	-1.12	-1.61	47.45	49.70	45.78
Pneumonia	33.21	33.65	21.03	1.19	1.72	0.28	136.40	125.28	95.55
Otitis media	350.29	135.06	33.86	43.32	17.41	4.19	1016.49	365.00	95.29
Deaths	0.12	0.11	0.16	-0.57	-0.56	-0.46	1.22	1.19	1.30
<b>Direct costs prevented</b>									
<b>Health care</b>	<b>€ 190,915</b>	<b>€ 167,747</b>	<b>€ 152,957</b>	<b>€ 12,708</b>	<b>-€ 25,038</b>	<b>-€ 19,334</b>	<b>€ 700,789</b>	<b>€ 713,714</b>	<b>€ 691,828</b>
Meningitis	€ 50,820	€ 47,450	€ 68,010	-€ 33,060	-€ 47,324	-€ 13,972	€ 341,700	€ 339,112	€ 397,391
Bacteremia	€ 6,694	€ 6,279	€ 8,013	-€ 14,139	-€ 14,584	-€ 11,050	€ 49,610	€ 49,886	€ 54,621
Other IPD	€ 17,540	€ 15,009	€ 14,567	-€ 24,961	-€ 29,137	-€ 36,165	€ 124,508	€ 134,107	€ 111,325
Pneumonia	€ 31,415	€ 33,143	€ 18,222	-€ 1,091	€ 369	€ 36	€ 330,321	€ 350,628	€ 279,286
Otitis media	€ 27,495	€ 10,643	€ 2,652	€ 3,332	€ 1,348	€ 350	€ 92,973	€ 37,309	€ 8,878
<b>Vaccination</b>	<b>-€ 1,027,222</b>	<b>-€ 1,027,222</b>	<b>-€ 1,483,010</b>	<b>-€ 1,027,222</b>	<b>-€ 1,027,222</b>	<b>-€ 1,483,010</b>	<b>-€ 1,027,222</b>	<b>-€ 1,027,222</b>	<b>-€ 1,483,010</b>
<b>Total</b>	<b>-€ 836,307</b>	<b>-€ 859,475</b>	<b>-€ 1,330,054</b>	<b>-€ 1,014,514</b>	<b>-€ 1,052,260</b>	<b>-€ 1,502,345</b>	<b>-€ 326,434</b>	<b>-€ 313,508</b>	<b>-€ 791,182</b>
<b>Quality-adjusted life-years gained</b>									
<b>Total</b>	<b>9.46</b>	<b>7.82</b>	<b>9.78</b>	<b>-7.22</b>	<b>-8.86</b>	<b>-4.10</b>	<b>50.38</b>	<b>47.14</b>	<b>50.50</b>
IPD	7.01	6.46	9.49	-9.41	-9.80	-4.34	47.32	44.80	50.06
Pneumonia	0.20	0.21	0.14	-0.01	0.00	-0.00	1.00	1.00	0.80
Otitis media	1.76	0.65	0.17	0.20	0.08	0.02	4.79	1.90	0.49
<b>Incremental Cost-Effectiveness Ratios (ICERs): Incremental direct costs per...</b>									
<b>IPD case averted</b>	€ 64,137	€ 65,621	€ 99,880	DOMINATED	DOMINATED	DOMINATED	€ 949,026	€ 892,729	€ 1,157,632
<b>Death averted</b>	€ 3,716,547	€ 3,758,016	€ 5,959,220	DOMINATED	DOMINATED	DOMINATED	€ 90,428,010	€ 59,969,690	€ 99,497,140
<b>Life-year gained</b>	€ 80,317	€ 81,737	€ 128,407	DOMINATED	DOMINATED	DOMINATED	€ 2,029,398	€ 1,284,264	€ 2,155,315
<b>QALY gained</b>	€ 68,893	€ 73,446	€ 105,608	DOMINATED	DOMINATED	DOMINATED	€ 584,828	€ 838,515	€ 1,401,835
<b>DALY averted</b>	€ 46,498	€ 48,295	€ 74,680	DOMINATED	DOMINATED	DOMINATED	€ 822,047	€ 647,729	€ 1,152,015

Dominated: additional costs versus the comparator, and at the same time worse health outcomes versus the comparator. Each row shows at the second and third main column heading, the 5th and 95th percentile of the variable distribution in that row, respectively. That is the values are given at each row from low to high. Since the distributions of costs and effects are correlated, comparisons between rows are not always straightforward. Since a substantial proportion of simulations yield the option under consideration to be dominated by the comparator, the rows with ICERs can be misleading and should be interpreted with care. Both the median and the 95th percentile are only indicative and represent underestimations (i.e. the ICERs of the simulations excluding domination are worse, see text for further explanation).

**Table 25. Estimated median costs and effects (and 95% interval) of pneumococcal conjugate vaccination with PCV10 or PCV13 in a 2+1 schedule versus the current situation (PCV7 in a 2+1 schedule), using current public pharmacy vaccine prices, a 5 year time span for infections to accrue, a wide ranging uniform distribution of serotype replacement, and including herd immunity effects (results of 1000 model iterations)**

	Median			5 <sup>th</sup> percentile			95 <sup>th</sup> percentile		
	PCV10 incl NTHI	PCV10 excl NTHI	PCV13	PCV10 incl NTHI	PCV10 excl NTHI	PCV13	PCV10 incl NTHI	PCV10 excl NTHI	PCV13
<b>Cases prevented</b>									
IPD	237	239	313	28	28	35	462	455	619
Pneumonia	195	192	181	26	24	21	540	538	594
Otitis media	5,937	2,241	546	703	276	66	11,571	4,473	1,217
Deaths	6.01	5.84	8.74	0.75	0.65	0.95	16.11	16.45	24.33
<b>Direct costs prevented</b>									
<b>Health care</b>	<b>€ 2,792,212</b>	<b>€ 2,477,435</b>	<b>€ 2,735,342</b>	<b>€ 859,735</b>	<b>€ 567,423</b>	<b>€ 531,792</b>	<b>€ 6,842,991</b>	<b>€ 6,304,337</b>	<b>€ 7,277,361</b>
Meningitis	€ 1,059,900	€ 1,038,204	€ 1,148,146	€ 104,175	€ 112,170	€ 127,975	€ 3,910,498	€ 3,760,922	€ 4,190,364
Bacteremia	€ 194,096	€ 187,881	€ 257,174	€ 18,602	€ 22,466	€ 29,402	€ 675,403	€ 677,087	€ 924,579
Other IPD	€ 371,692	€ 361,639	€ 533,770	€ 40,712	€ 37,165	€ 52,752	€ 1,631,806	€ 1,871,907	€ 2,613,144
Pneumonia	€ 196,448	€ 193,369	€ 216,151	€ 13,693	€ 12,648	€ 9,282	€ 1,667,052	€ 1,602,533	€ 1,702,908
Otitis media	€ 466,804	€ 176,830	€ 43,123	€ 55,129	€ 22,291	€ 5,729	€ 941,486	€ 377,788	€ 104,147
<b>Vaccination</b>	<b>-€ 1,416,906</b>	<b>-€ 1,416,906</b>	<b>-€ 2,774,361</b>	<b>-€ 1,416,906</b>	<b>-€ 1,416,906</b>	<b>-€ 2,774,361</b>	<b>-€ 1,416,906</b>	<b>-€ 1,416,906</b>	<b>-€ 2,774,361</b>
<b>Total</b>	<b>€ 1,375,306</b>	<b>€ 1,060,529</b>	<b>-€ 39,020</b>	<b>-€ 557,171</b>	<b>-€ 849,483</b>	<b>-€ 2,242,569</b>	<b>€ 5,426,086</b>	<b>€ 4,887,432</b>	<b>€ 4,503,000</b>
<b>Quality-adjusted life-years gained</b>									
<b>Total</b>	210.53	195.58	226.45	50.43	32.35	28.81	501.13	514.96	590.60
IPD	181.50	184.82	222.44	22.89	19.53	24.27	470.50	495.51	587.19
Pneumonia	1.31	1.29	1.26	0.17	0.17	0.12	4.88	4.75	5.52
Otitis media	29.21	10.98	2.66	3.45	1.30	0.35	60.24	24.21	6.34
<b>Incremental Cost-Effectiveness Ratios (ICERs): Incremental direct costs per...</b>									
Life-year gained	DOMINANT	DOMINANT	€ 140	DOMINANT	DOMINANT	DOMINANT	€ 21,363	€ 36,679	€ 89,974
QALY gained	DOMINANT	DOMINANT	€ 176	DOMINANT	DOMINANT	DOMINANT	€ 9,810	€ 20,324	€ 72,647
DALY averted	DOMINANT	DOMINANT	€ 157	DOMINANT	DOMINANT	DOMINANT	€ 13,277	€ 21,630	€ 64,319

Dominant: direct cost-savings versus the comparator, and at the same time gaining health outcomes versus the comparator. Each row shows at the second and third main column heading, the 5<sup>th</sup> and 95<sup>th</sup> percentile of the variable distribution in that row, respectively. That is the values are given at each row from low to high. Since the distributions of costs and effects are correlated, comparisons between rows are not always straightforward (e.g., the row total costs prevented (direct health care costs, net of vaccination costs) is shown from low (worst) to high (best), whereas the ICERs are in their row also shown from low (best) to high (worst)).



**Table 26. Estimated median costs and effects (and 95% interval) of pneumococcal conjugate vaccination with PCV10 or PCV13 in a 3+1 schedule versus the current situation (PCV7 in a 2+1 schedule), using current public pharmacy vaccine prices, a 5 year time span for infections to accrue, a wide ranging uniform distribution of serotype replacement, and including herd immunity effects (results of 1000 model iterations)**

	Median			5 <sup>th</sup> percentile			95 <sup>th</sup> percentile		
	PCV10 incl NTHI	PCV10 excl NTHI	PCV13	PCV10 incl NTHI	PCV10 excl NTHI	PCV13	PCV10 incl NTHI	PCV10 excl NTHI	PCV13
<b>Cases prevented</b>									
IPD	258	258	328	29	29	37	494	488	656
Pneumonia	232	236	209	30	29	23	676	624	678
Otitis media	6317	2373	587	764	292	71	12300	4773	1310
Deaths	6.2	6.1	8.9	0.8	0.7	1.0	16.3	17.1	25.0
<b>Direct costs prevented</b>									
<b>Health care</b>	<b>€ 3,019,123</b>	<b>€ 2,679,600</b>	<b>€ 2,919,034</b>	<b>€ 922,919</b>	<b>€ 624,909</b>	<b>€ 561,173</b>	<b>€ 7,253,166</b>	<b>€ 6,845,721</b>	<b>€ 7,796,287</b>
Meningitis	€ 1,125,439	€ 1,086,583	€ 1,242,611	€ 110,343	€ 120,631	€ 131,522	€ 4,214,675	€ 3,939,856	€ 4,612,005
Bacteremia	€ 204,936	€ 196,322	€ 268,551	€ 18,705	€ 23,291	€ 30,966	€ 726,062	€ 702,337	€ 957,901
Other IPD	€ 395,881	€ 387,907	€ 550,947	€ 44,507	€ 40,106	€ 56,163	€ 1,705,564	€ 1,935,632	€ 2,698,084
Pneumonia	€ 234,152	€ 237,378	€ 235,822	€ 14,693	€ 14,522	€ 9,948	€ 1,920,880	€ 1,964,777	€ 1,989,925
Otitis media	€ 499,199	€ 188,119	€ 46,190	€ 59,370	€ 23,544	€ 6,387	€ 994,817	€ 399,032	€ 110,813
<b>Vaccination</b>	<b>-€ 2,444,128</b>	<b>-€2,444,128</b>	<b>-€4,257,372</b>	<b>-€2,444,128</b>	<b>-€2,444,128</b>	<b>-€4,257,372</b>	<b>-€ 2,444,128</b>	<b>-€ 2,444,128</b>	<b>-€ 4,257,372</b>
<b>Total</b>	<b>€ 574,995</b>	<b>€ 235,471</b>	<b>-€1,338,338</b>	<b>-€1,521,209</b>	<b>-€1,819,220</b>	<b>-€3,696,198</b>	<b>€ 4,809,038</b>	<b>€ 4,401,593</b>	<b>€ 3,538,915</b>
<b>Quality-adjusted life-years gained</b>									
<b>Total</b>	<b>223.98</b>	<b>211.83</b>	<b>238.09</b>	<b>53.76</b>	<b>34.72</b>	<b>30.98</b>	<b>518.34</b>	<b>539.09</b>	<b>625.08</b>
IPD	192.37	196.24	231.19	23.28	21.13	26.17	474.41	525.28	618.55
Pneumonia	1.55	1.56	1.46	0.18	0.19	0.13	5.72	5.69	6.18
Otitis media	31.49	11.70	2.86	3.64	1.42	0.37	64.56	25.64	6.81
<b>Incremental Cost-Effectiveness Ratios (ICERs): Incremental direct costs per...</b>									
<b>Life-year gained</b>	DOMINANT	DOMINANT	€ 5,653	DOMINANT	DOMINANT	DOMINANT	€ 59,072	€ 74,398	€ 152,446
<b>QALY gained</b>	DOMINANT	DOMINANT	€ 4,950	DOMINANT	DOMINANT	DOMINANT	€ 25,583	€ 43,784	€ 115,124
<b>DALY averted</b>	DOMINANT	DOMINANT	€ 4,390	DOMINANT	DOMINANT	DOMINANT	€ 34,748	€ 48,072	€ 101,289

Dominant: direct cost-savings versus the comparator, and at the same time gaining health outcomes versus the comparator. Each row shows at the second and third main column heading, the 5<sup>th</sup> and 95<sup>th</sup> percentile of the variable distribution in that row, respectively. That is the values are given at each row from low to high. Since the distributions of costs and effects are correlated, comparisons between rows are not always straightforward (e.g. the row total costs prevented (direct health care costs, net of vaccination costs) is shown from low (worst) to high (best), whereas the ICERs are in their row also shown from low (best) to high (worst)).

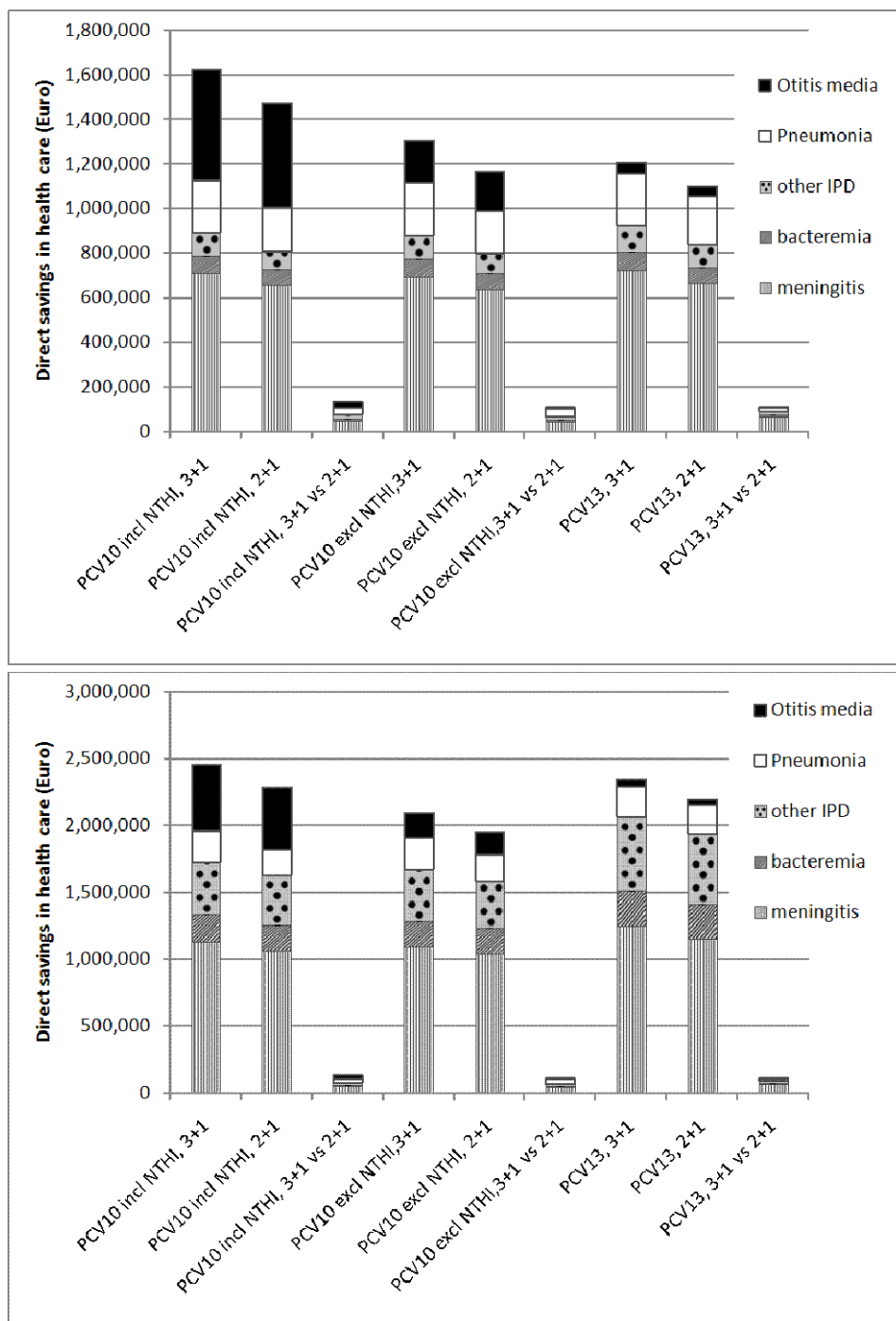
Tables 22 to 26 show many outcomes including cost-effectiveness ratios, direct net savings, savings in treatment costs and QALYs gained per specific disease state for PCV10 and PCV13 using various schedules of vaccination. Given the assumed differential impact of the vaccines (mainly in relation to AOM) and above all the price difference of current pharmacy prices, PCV10 is estimated to avoid more treatment costs but gain fewer QALYs than PCV13. If AOM is ignored, PCV13 avoids more treatment costs and gains more QALYs. Therefore on average, given equal vaccine prices, PCV13 is preferable to PCV10 when one only considers the impact these vaccines have on IPD and pneumonia. In the above tables, one can also read how the savings in treatment costs and the gains in QALYs are distributed over the various clinical disease expressions, distinguishing between meningitis, bacteremia, other IPD, pneumonia and otitis media.

A visual representation of these data is also shown in figures 18 and 19 of the median savings in health care treatment (i.e. without vaccination costs), and the median QALYs gained, respectively. Caution is needed when reading these figures, as we present medians per specific clinical disease state, and not the entire distribution around the median (which is also given in table 22). It should be easy for the reader to imagine the bars in figures 18 and 19 without the top section, which is the contribution of AOM to the estimates presented. Thus it allows the reader to consider the model's estimated differential effectiveness of PCV10 and PCV13, given different scenarios (with and without AOM, AOM with and without NTHI, each with and without herd immunity). It is important to remember that these results are presented with the influential assumption that serotype replacement ranges uniformly between 0% (no STR) and 99% (near complete STR), and that the same % change in STR signifies in the model that relatively more serotypes need to be replaced for PCV13 than for PCV10 in relation to IPD.

It seems clear though that due to the high caseload of AOM, the main impact of AOM would be in treatment costs saved, and to a much lesser extent in QALYs gained, relative to IPD (the main reason being that QALYs are combined measures of morbidity and mortality, and deaths in children, as well as children with long term sequelae (which are included in these estimates), weigh heavier in the estimates than the transient QALY impact of most episodes of AOM. Relative to pneumonia, it is important to remember that the efficacy estimates for pneumonia are very close for both vaccines (despite using a more favorable estimate for PCV10 than for PCV13), and the difference in QALY decrement per case with AOM is small for non-hospitalised pneumonia (0.001 difference per case while the AOM caseload is more than sevenfold that of pneumonia in children, see figure 10).

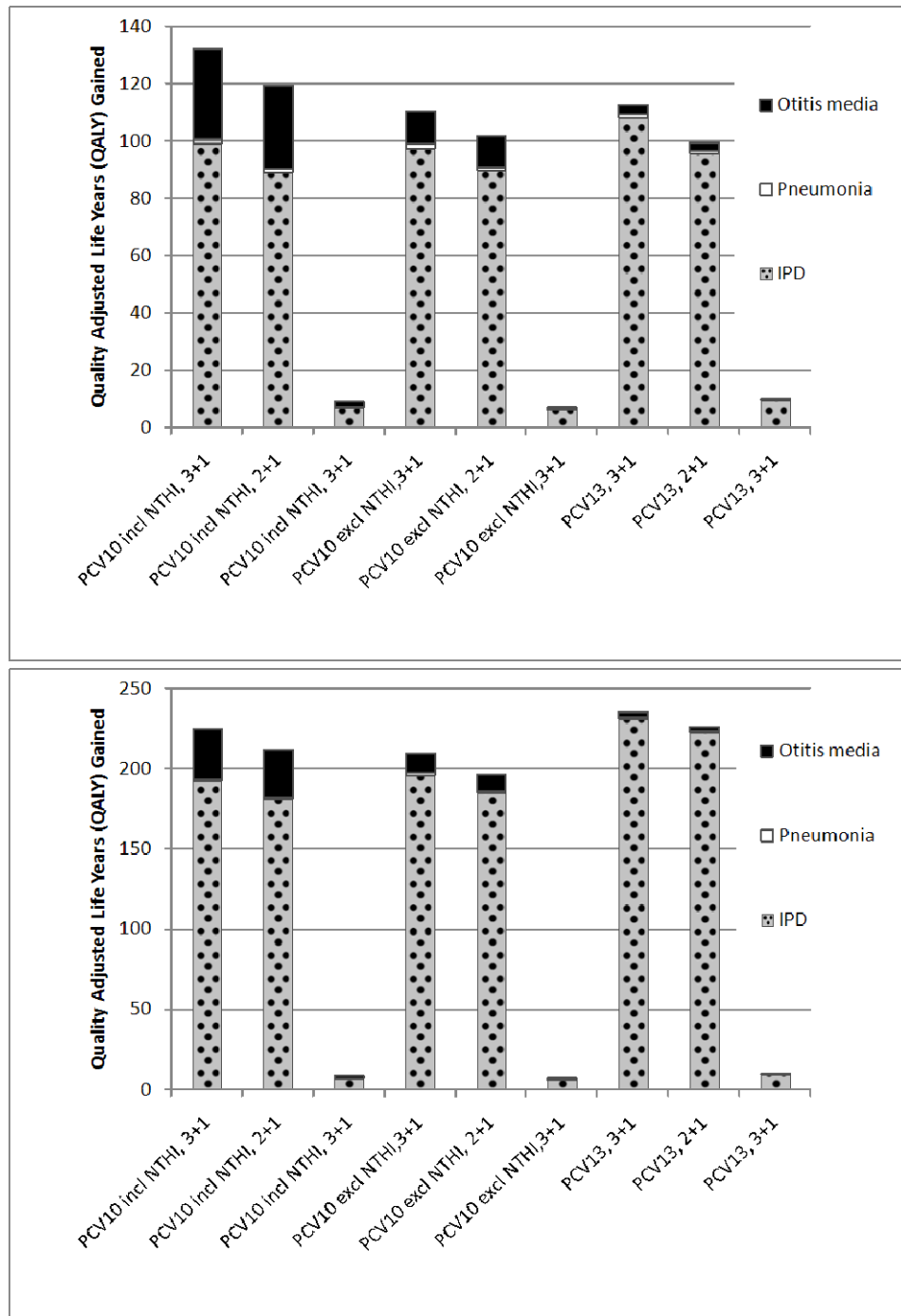
In what follows, we return to this issue several times by extensive scenario analyses, with and without AOM, and with varying degrees of effectiveness against AOM, as well as varying degrees of STR.

**Figure 18. Median direct savings (€) in treatment costs, according to clinical manifestation for different decisional viewpoints on PCV10 or PCV13, including wide ranging uncertainty on serotype replacement on all clinical manifestations**



Top panel: excluding herd immunity, bottom panel: including herd immunity for IPD only

**Figure 19. Median QALY gains according to clinical manifestation for different decisional viewpoints on PCV10 or PCV13, including wide ranging uncertainty on serotype replacement on all clinical manifestations**



Top panel: excluding herd immunity, bottom panel: including herd immunity for IPD only

### 8.3.3 Further scenario analyses

The impact of other analytical choices are shown by scenario analyses in table 27 below. It is shown that none of these scenarios have an impact that can match the impact of ignoring AOM (and thus focusing exclusively on these vaccines ability to prevent pneumonia and IPD).

**Table 27. Additional scenario analyses at price parity (based on 1000 simulations at each row). Median direct costs (€) per QALY gained (5<sup>th</sup> percentile, 95<sup>th</sup> percentile)**

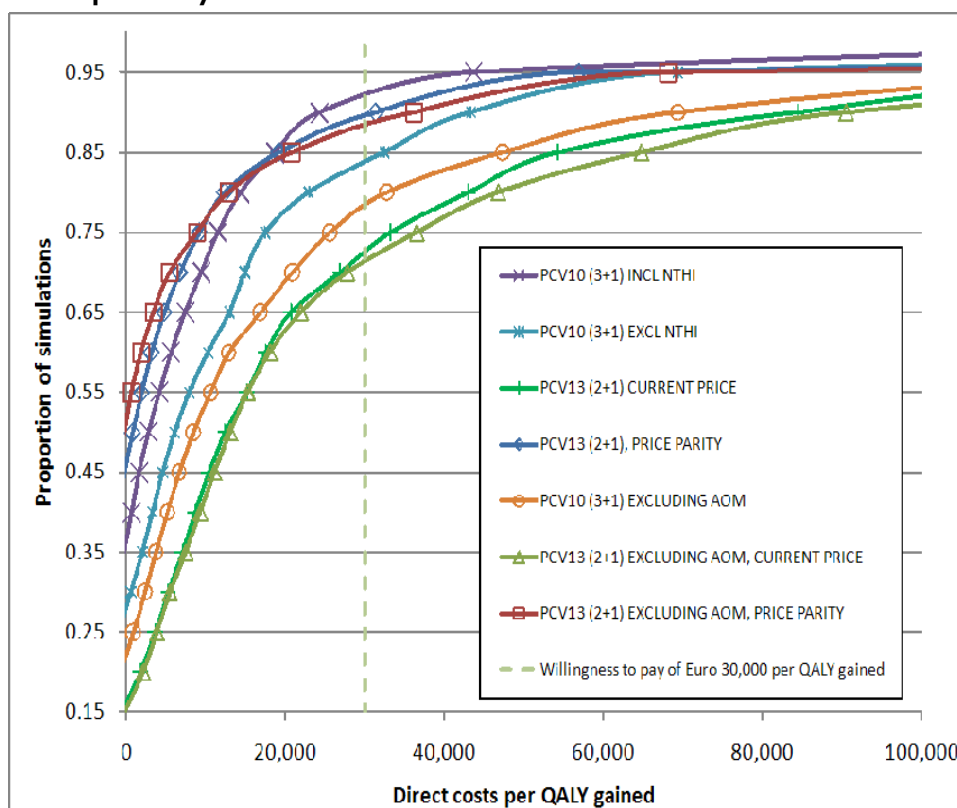
	EXCLUDING HERD IMMUNITY		INCLUDING HERD IMMUNITY	
	PCV10 (3+1) vs. PCV7 (2+1)	PCV13 (2+1) vs. PCV7 (2+1)	PCV10 (3+1) vs. PCV7 (2+1)	PCV13 (2+1) vs. PCV7 (2+1)
<b>“Base”</b>	3,064 (Dominant, 41,641)	217 (Dominant, 58,451)	Dominant (Dominant, 27,300)	Dominant (Dominant, 24,091)
<b>Excluding acute otitis media</b>	8,549 (Dominant, 125,737)	402 (Dominant, 70,202)	Dominant (Dominant, 61,335)	Dominant (Dominant, 23,857)
<b>Discounting costs and effects at 3%</b>	4,183 (Dominant, 50,744)	263 (Dominant, 77,618)	Dominant (Dominant, 29,495)	Dominant (Dominant, 28,379)
<b>No waning of dose specific efficacy</b>	2,862 (Dominant, 37,402)	Dominant (Dominant, 52,446)	Dominant (Dominant, 22,428)	Dominant (Dominant, 20,844)
<b>10 year time span for infection to accrue</b>	908 (Dominant, 31,878)	Dominant (Dominant, 49,996)	Dominant (Dominant, 21,016)	Dominant (Dominant, 19,350)

“base”: efficacy against IPD based on OPA measurements, wide ranging distribution on serotype replacement (0-99%); 5 year time span; discounting costs at 3% and effects at 1.5%, including vaccine-specific efficacy on otitis media (including otitis media caused by NTHI), assuming dose-specific waning. Price parity: price PCV13 = current pharmacy price PCV10

### 8.3.4 Influence of vaccine price and of inclusion or exclusion of AOM

PCV10 is estimated to be more cost-effective than PCV13 at the current price level (with PCV13's public price per dose currently exceeding that of PCV10 by €4.11). However, at price parity (i.e. assuming PCV13's incremental price over PCV7 drops to that of PCV10), the cost-effectiveness is quite similar with both CEACs crossing. If additionally we exclude the differential impact of the vaccines on otitis media, the balance tips clearly, as expected from the serotype coverage of both vaccines, in favour of PCV13 (see figure 20).

**Figure 20. Influence of price parity and of inclusion or exclusion of AOM**  
**Cost-effectiveness acceptability curves (€) for a 2+1 schedule with PCV13 or**  
**a 3+1 schedule with PCV10 versus the current situation, assuming no herd**  
**immunity effects, a wide ranging distribution of serotype replacement, and a**  
**time span of 5 years**



Price parity: the price of PCV13 is set equal to that of PCV10

When comparing PCV10 in a 3+1 versus PCV13 in a 2+1 schedule in more detail, we found that PCV10 is likely to be more cost-effective than PCV13, if efficacy against NTHI OM is included and herd immunity effects (IPD only) are excluded. Using current public pharmacy prices and excluding herd immunity, PCV10 in a 3+1 schedule (including efficacy against NTHI OM) was found to be dominant (i.e. less costly and more effective) over PCV13 in a 2+1 schedule in 93% of the simulations, whereas it was found to have an incremental cost-effectiveness ratio over PCV13 of less than €30,000 per QALY gained in another 3% of simulations (i.e. PCV10 was likely to be considered more preferable in 96% of the simulations). When using the same price per dose for PCV13 as for PCV10, and including PCV10's efficacy against NTHI OM, these percentages decreased to 16% and 49%, respectively (i.e. PCV10 was likely to be considered more preferable in 65% of the simulations). When herd immunity for IPD was included, these percentages were 5% and 23% at price parity, and PCV13 was then dominant in 48% of the simulations and had a likely acceptable ICER in another 24% of the simulations (thus making PCV13 preferable in 72% of the simulations). When PCV10's efficacy against NTHI OM was excluded, a similar pattern emerged. PCV10 was likely to be preferable at current prices (in 88% and 51% of the simulations without and with herd immunity, respectively), and PCV13 was likely to be preferable at price parity (in 77% and 96% of the simulations without and with herd immunity, respectively). Clearly, the prices at which both vaccine formulations are offered in large quantities will determine to a large extent the choice between them.

Additionally, considerations of the relative importance one wishes to give to preventing mild disease in many children (i.e. AOM) versus preventing very severe disease in rare cases (i.e. IPD) may also determine how one wishes to approach the choice between these two vaccines.

Because as clearly shown in this section and the previous section, the inclusion or exclusion of differential AOM impacts of PCV10 versus PCV13 has a decision changing influence (as they have been reported in the medical literature, see review sections and input data section)

### 8.3.5 Influence of serotype replacement and herd immunity assumptions

At constant prices, the direct costs per life-year and per QALY gained are most sensitive to STR (using linear regression it explains between 50% and 70% of the variation in direct costs per QALY gained, for scenarios with and without herd immunity). For both PCV10 and PCV13, STR of IPD is more influential than STR of AOM (and the latter is more influential for PCV10). This is not surprising in view of the distribution of avoided treatment costs and QALYs gained over the various disease states (cf. figures 18 and 19). Additionally, the extent PCV10 protects against AOM (i.e. whether or not efficacy against AOM due to NTHI, or against any AOM is included) dominates other parameter uncertainty.

When we assume no STR would occur, then all simulations for PCV10 and PCV13 in a 2+1 or a 3+1 schedule versus the current situation have an ICER below €30,000 per QALY gained, even if we assume that these vaccines offer no additional protection against AOM. The inclusion of herd immunity effects clearly has a positive impact, even in the presence of serotype replacement. If in addition to the effect of herd immunity, STR is assumed not to occur, then PCV10 and PCV13 become cost-saving.

### 8.3.6 Joint influence of vaccine price, expected serotype replacement and of the additional effectiveness of PCV10 versus PCV13 against otitis media

In view of the importance of price differences we explore this issue further in figure 21. When we assume there would be no serotype replacement at all, and there would be no additional impact of PCV10 on AOM over and above that of PCV13, the health care payer can afford to pay more for PCV13 than for PCV10 without losing in cost-effectiveness (figure 21).

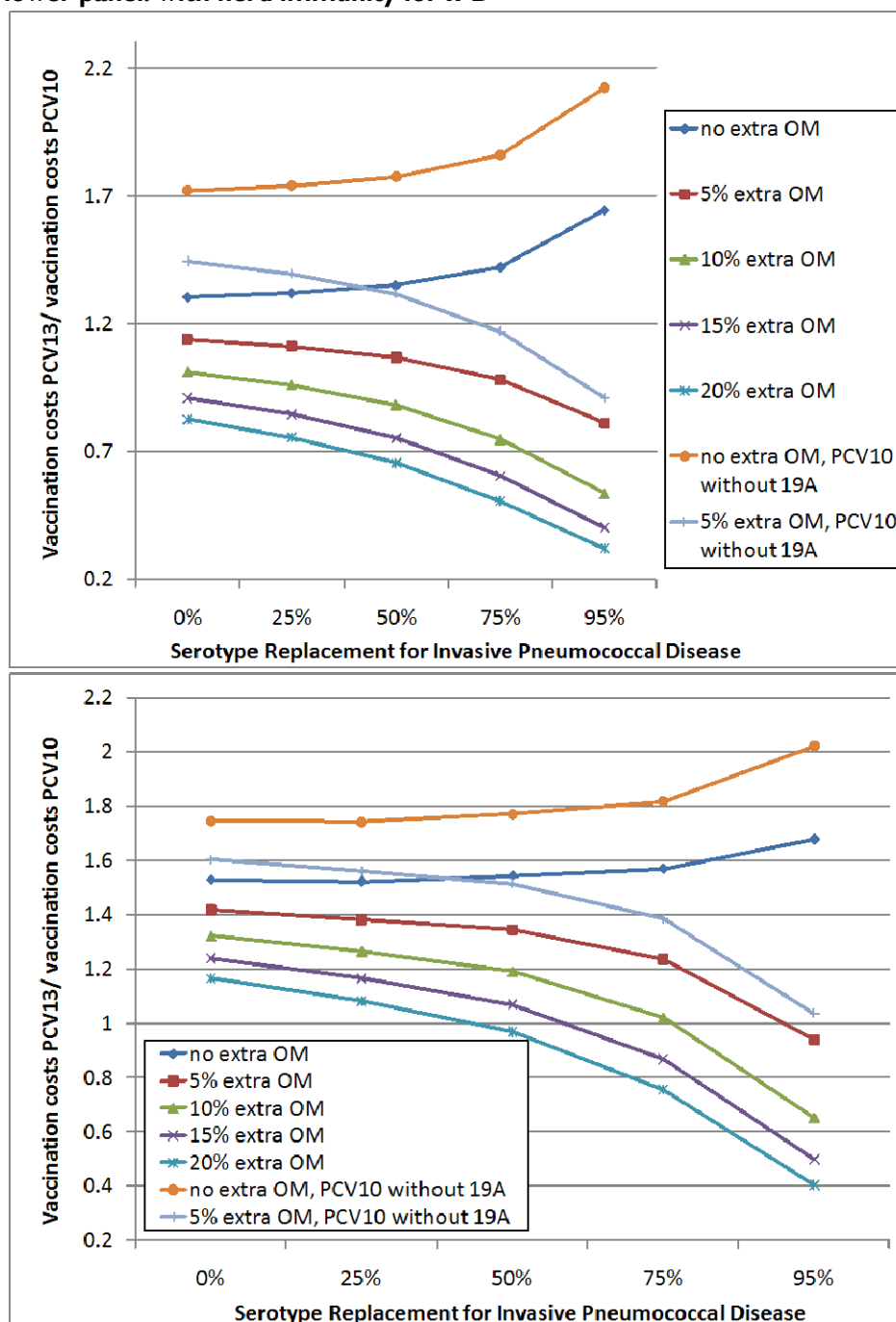
In more realistic scenarios in which there is a higher impact on AOM from PCV10 versus PCV13, PCV13 can still be priced higher, if it is expected that herd immunity effects would occur mainly for IPD, and serotype replacement remains low. If PCV10 yields 10% higher effectiveness against AOM, then the advantage is reversed, especially when we expect at the same time large serotype replacement effects. For instance in the absence of herd immunity and serotype replacement, and for an additional reduction in AOM of 10% with PCV10 versus PCV13, the additional price for PCV13 (over and above PCV7) can be about 1.1% (price ratio 1.011) higher than the additional price for PCV10 (over and above PCV7) before it is no longer preferable on the basis of cost-effectiveness. With increasing serotype replacement in invasive pneumococcal disease (only), the advantage of PCV13 over PCV10 decreases when PCV10 induces additional effectiveness against AOM (e.g. at 50% STR, the price should be about 88% of that of PCV10, assuming additional AOM efficacy of 10%). If PCV10 and PCV13 are equally effective against AOM (i.e. “no extra AOM” in figure 21), then increasing serotype replacement will further increase the ratio in the PCV13 price versus the PCV10 price, to the advantage of PCV13 (see figure 21). This is due to the fact that the additional dose under the 3+1 schedule for PCV10 comes at a fixed additional administration cost. Therefore, in order to sustain a constant acceptable cost-effective ratio with increasing serotype replacement for IPD, the purchase price per dose is driven down more rapidly for PCV10 (3+1 schedule in figure 21) than for PCV13 (2+1 schedule in figure 21). If the increase in serotype replacement would occur also for pneumonia and AOM, the ratio between the prices of the different vaccines would remain relatively stable (because their effectiveness would be impaired for the different clinical manifestations of pneumococcus to the same extent).

Figure 21 is subject to the limitation that serotype replacement is modeled as the % replacement of serotypes covered by each vaccine separately. This implies the same % change in STR in figure 24 indicates (slightly) more replacement of pneumococcal serotypes for PCV13 than for PCV10. Note that most of the simulations elaborated above assume through their distributions implicitly an average serotype replacement of 49.5%, and that PCV10 is assumed (based on the literature) to provide protection against 10% extra AOM including NTHI, and about 3% extra AOM excluding NTHI (see also data and methods section 8.2 above). In view of the large influence of serotype replacement, if it were to occur more rapidly or more extensively for one of these new PCV vaccines, then it would clearly create a large advantage for the other vaccine.

A specific concern in respect to serotype replacement is related to serotype 19A, which was noted in Belgium and other European countries for its rapid emergence in the pre- and post-PCV7 period. It is currently the single serotype which causes the highest percentage of pneumococcal meningitis cases (see also table 7). As outlined in the review sections of this report, it can be disputed whether PCV10 would offer cross protection against serotype 19A, whereas for PCV13 the evidence for direct protection against serotype 19A is clear. Therefore we have shown for key outcomes only (in an effort to limit the amount of output tables and figures) the impact of using the “average” effectiveness approach, excluding cross protection from serotype 19A for PCV10, rather than the OPA-based approach (which is based on an expected correlation between protective efficacy and % of OPA responders). We show this 19A impact also in figure 21, indicating that it yields estimates which are clearly more favorable to PCV13.



Figure 21. Ratio of additional vaccine price per dose of PCV13 in a 3+1 schedule versus PCV10 in a 2+1 schedule at which both vaccines are equally cost-effective (at €30,000 per QALY gained), in relation to expected serotype replacement and the additional effectiveness of PCV10 versus PCV13 against otitis media. Upper panel: without herd immunity for IPD; lower panel: with herd immunity for IPD



A limitation of our model might be that serotype replacement is uniformly implemented and the serotype distribution is prevalence based, without formal quantification of the fact that some specific serotypes may rise more rapidly, or be more pathogenic than others. This might be specifically relevant for emerging serotypes for which both vaccines' effectiveness is potentially different (e.g., serotype 19A). However, it remains unpredictable whether (1) past trends in serotype distribution will continue in the future; (2) more, similarly, or less pathogenic serotypes will occupy the ecological space of the vaccine serotypes they may (or may not) replace.

Therefore, given our current state of knowledge, the parameterization of such additional serotype specific considerations remains problematic. Nonetheless this limitation should be considered alongside the estimations produced in this report.

### 8.3.7 Budget impact analysis

Developing a budget-impact analysis in the absence of intervention costs (which will be very much determined by the prices after a competitive tendering process) is highly speculative. Indeed, it is likely that both vaccines are offered at a lower price than PCV7. Since they both are more effective than current practice (and likely cheaper to buy), their introduction would lead to cost-savings. These savings would occur immediately, from the first year of introduction onwards. That is, of course, unless the schedule is changed to a 3+1 schedule, which would adversely impact on the vaccine quantity purchased, and the required administration costs to deliver the extra dose.

For the sake of illustration, if we assume that both vaccines are equally priced at the current pharmacy price of PCV10, and PCV13 is given in a 2+1 schedule, and PCV10 in a 3+1 schedule, then the budget development over the first five years is as illustrated in table 28. The reason why these costs peak in the third and fourth year, is that in those years, we would have vaccinated 3 (4) extra cohorts, but the main benefits arising to these vaccinated cohorts have not accrued yet (these will follow over longer time periods).

PCV10 has a larger impact on the evolution of the budget, due to the additional dose required, and the additional administration costs to deliver this extra dose (in the illustration we use the AOM impact including NTHI in the benefits attributed to PCV10).

**Table 28. Evolution of mean additional annual health care costs (€) over the first 5 years, assuming both vaccines would be purchased at a higher price than PCV7 (price PCV13 = current pharmacy price of PCV10)**

Year after introduction	PCV13, 2+1, discounted	PCV13, 2+1, undiscounted	PCV10, 3+1, discounted	PCV10, 3+1, undiscounted
0	618,116	618,116	1,471,733	1,471,733
1	893,964	920,783	2,425,111	2,497,864
2	965,524	1,024,325	3,010,533	3,193,874
3	895,282	978,299	3,309,889	3,616,806
4	677,015	761,987	3,333,739	3,752,153

## 9 CONCLUSION

In June 2006 a previous KCE report<sup>4</sup> examined the pre-vaccination disease burden and the potential effectiveness and cost-effectiveness of childhood vaccination using “Prevenar ®” the then licensed PCV7 vaccine, which was first introduced in the US universal infant vaccination programme in 2000. It concluded that the cost-effectiveness of universal infant PCV7 vaccination in Belgium is uncertain due to the uncertainties arising out of herd immunity effects and serotype replacement.<sup>4</sup> It argued, however, that the uncertainty, in terms of cost-effectiveness, would be lower using a 2+1 schedule, than a 3+1 schedule. It showed that the incremental cost-effectiveness of using the 3+1 versus the 2+1 schedule was likely unfavourable.

From January 2007 onwards, the 2+1 option was implemented in the universal infant vaccination programmes of the Belgian communities, with catch up vaccination for children up to 2 years of age.

In 2009, two new conjugate vaccines were licensed in Europe. One is 10-valent (PCV10), containing antigens from the same seven serotypes as the currently widely used seven-valent vaccine (PCV7) together with capsular polysaccharide antigens from serotypes 1, 5 and 7F. They are conjugated for 8 of them to a surface protein D from *Haemophilus influenzae* and for 2 of them to modified Diphtheria toxin and Tetanus toxoid, respectively. PCV10 is licensed to be used in a schedule with three priming doses and a booster dose only (3+1 schedule). The other one is 13-valent (PCV13), and contains in addition to the seven serotypes in PCV7 capsular polysaccharide antigens from serotypes 1, 3, 5, 6A, 7F and 19A, all conjugated to the modified Diphtheria toxin.<sup>9</sup> PCV13 is licensed to be used in either a schedule with three priming doses and a booster dose (i.e. vaccine doses at ages 2, 3, 4 and 12 months, or the 3+1 schedule) or a schedule with 2 priming doses and a booster dose (i.e. vaccine doses at ages 2, 4 and 12 months, or the 2+1 schedule).

Although PCV13 is expected to provide protection against non-invasive disease caused by *S. pneumoniae* (additionally to PCV7), it is focused on preventing invasive disease caused by the six additional vaccine serotypes. PCV10 is relatively more focused on preventing more otitis media than PCV7, and is expected to be able to do this for OM caused by both *S. pneumoniae* and NTHI. There is uncertainty about PCV10's potential to reduce IPD caused by serotype 19A, which is a serotype of particular concern since it has become more and more prevalent over recent years. There is limited clinical trial data for PCV10 and PCV13, as most of the trials aimed to demonstrate immunogenicity, safety and tolerability of these vaccines, and clinical effectiveness is inferred from these immunological data, based on earlier vaccine formulations.

In view of the availability of PCV10 and PCV13, in the current report we aimed to estimate the incremental effectiveness and cost-effectiveness of replacing PCV7 by either PCV10 or PCV13 in Belgium.

In order to do this, we developed a simulation model which can mimic the incidence and consequences of pneumococcal infections in cohorts of vaccinated children as well as in the general population, and the direct and indirect impact of PCV10 and PCV13 relative to PCV7. We also reviewed Belgian data sources, and the international literature to parameterise the model to our best ability.

The main limitations of our model are as follows:

- We do not model the consequences of serotype replacement on individual serotypes nor the pathogenicity by serotype,
- We do not account for antibiotic resistance (again a problem for which serotype 19A is a cause for concern),
- We do not attempt to model the transmission dynamics of pneumococcal serotypes.

The main strengths of our approach are as follows:

- We take account of serotype replacement and herd immunity separately, because they are two different indirect aspects of PCV10 or PCV13 vaccination,
- We compare tens of different scenarios for estimating the comparative effectiveness and cost-effectiveness of these vaccines,
- We make an extensive threshold price comparison for PCV10 and PCV13, in relation to serotype replacement, herd immunity, cross protection and the extent PCV10 offers additional protection against otitis media versus PCV13.

It is noteworthy that our literature review retrieved no modeling studies that attempted to make projections of the impact of PCV10 or PCV13 considering any of the aspects we listed here under main strengths, nor those listed under weaknesses.

The analysis and interpretation of results is made difficult due to the uncertain nature of the speed and extent of serotype replacement, as well as herd immunity (i.e. the indirect protection of unvaccinated persons (e.g., immunocompromised children, adults and elderly) due to the reduced circulation of pathogens following widespread vaccination of children). These aspects were considered in the simulations and shown to be highly influential for the results. We consider it a strength of the analysis that – for the first time internationally - the model is flexible in using and comparing various correlates of protection by vaccine serotype (ELISA-based and OPA-based versus the hitherto widely used “average approach”).

Using a variety of approaches and schedules to estimate the effectiveness of PCV10 and PCV13 versus IPD, otitis media and pneumonia, as well as including or excluding large serotype replacement effects, and/or herd immunity effects, the results were robust to show that both vaccines are highly likely to be cost-saving or considered cost-effective versus PCV7 at their current public pharmacy prices (the current price for PCV7, PCV10 and PCV13 is €66.15, €70.44 and €74.55 per dose, respectively). The incremental cost-effectiveness of the 3+1 schedule versus the 2+1 schedule is high and uncertain for both vaccines (with the 3+1 schedule being dominated (i.e. less effective, more costly) by the 2+1 schedule in 10.8% of simulations and none of the simulations yielding direct costs per QALY gained of less than €30,000). Therefore the 3+1 schedule is highly unlikely to be judged a worthwhile option, if the vaccine price per dose is constant between schedules. The comparison between 3+1 and 2+1 is only relevant at present for PCV13, which is licensed for both schedules (and PCV10 only for the 3+1 schedule). Note that we assume that both schedules would yield the same herd immunity effects. If the 3+1 schedules would yield substantially more herd immunity or provoke less STR, then it could lower the ICER of the 3+1 versus the 2+1 schedule to a level where it may become acceptable. However, at present, the evidence from post-PCV7 observational studies suggests there is no differential impact of a reduced schedule on either of these indirect aspects.

In short, it seems clear, that even at current pharmacy prices, both vaccines are likely to be judged preferable to the current situation, and therefore one of these two new vaccines should replace PCV7. What is far less clear though – as shown extensively in this report – is which vaccine of these two vaccines should be chosen.

At the current pharmacy prices, PCV13 is less likely to be cost-effective than PCV10. However after a tender procedure the price differences between both vaccines will change.

When comparing PCV10 in a 3+1 versus PCV13 in a 2+1 schedule, we found that PCV10 is likely to be more cost-effective than PCV13, if efficacy against NTHI OM is included and herd immunity effects (for IPD only) are excluded. Using current public pharmacy prices and excluding herd immunity, PCV10 in a 3+1 schedule (including efficacy against NTHI OM) was found to be dominant (i.e. less costly and more effective) over PCV13 in a 2+1 schedule in 93% of the simulations, whereas it was found to have an incremental cost-effectiveness ratio over PCV13 of less than €30,000 per QALY gained in another 3% of simulations (i.e. PCV10 was likely to be considered more preferable in 96% of the simulations).

When using the same price per dose for PCV13 as for PCV10, these percentages decreased to 16% and 49%, respectively (i.e. PCV10 was likely to be considered more preferable in 65% of the simulations). When herd immunity for IPD was included, these percentages were 5% and 23% at price parity, and PCV13 was then dominant in 48% of the simulations and had a likely acceptable ICER in another 24% of the simulations (thus making PCV13 preferable in 72% of the simulations). When PCV10's efficacy against NTHI OM was excluded, a similar pattern emerged. PCV10 was likely to be preferable at current prices (in 88% and 51% of the simulations without and with herd immunity, respectively), and PCV13 was likely to be preferable at price parity (in 77% and 96% of the simulations without and with herd immunity, respectively). Clearly, the prices at which both vaccine formulations are offered in large quantities will determine to a large extent the choice between them. Additionally, considerations of the relative importance one wishes to give to preventing mild disease in many children (i.e. AOM) versus preventing very severe disease in rare cases (i.e. IPD) may also determine how one wishes to approach the choice between these two vaccines.

The direct costs per life-year and per QALY gained are most sensitive to STR. For both PCV10 and PCV13, STR of IPD is more influential than STR of AOM (and the latter is more influential for PCV10). Additionally, the extent PCV10 protects against AOM (i.e. whether or not efficacy against AOM due to NTHI, or against any AOM is included) dominates other parameter uncertainty. Other aspects, tested in scenarios, such as the correlate of protection basis for the effectiveness estimates, the time span for infections to accrue, the discount rates, the dose-specific waning scenarios have all near negligible impacts by comparison to AOM and STR.

The choice between PCV10 and PCV13 will also be driven by adaptability in the Belgian schedule (currently 2+1 schedule), and concerns about IPD caused by one specific serotype (serotype 19A), which has been rising in the recent past. PCV13 is likely to provide high protective efficacy against IPD caused by 19A, whereas this is less clear for PCV10. Furthermore, the price differences between both vaccines, that will arise out of a competitive tendering process will undoubtedly be of paramount importance in the choice between both vaccines.

In sum, we showed that it is the combined uncertainty of differences in price, effectiveness against AOM, and likely serotype replacement impact that will determine (almost completely) the cost-effectiveness preference base for either PCV10 or PCV13. We also showed that there is a sufficient evidence base for a decision to replace the current vaccine, PCV7, by either one of these vaccines.

## 10 APPENDICES: ADDITIONAL COST-EFFECTIVENESS ACCEPTABILITY CURVES

Figure a. Cost-effectiveness acceptability curves (€) for PCV10 (2+1 schedule) versus current situation (PCV7, 2+1 schedule), current public vaccine prices, serotype replacement for invasive pneumococcal disease, pneumonia and otitis media and a time span of 5 years, upper panel: no herd immunity, lower panel: with herd immunity

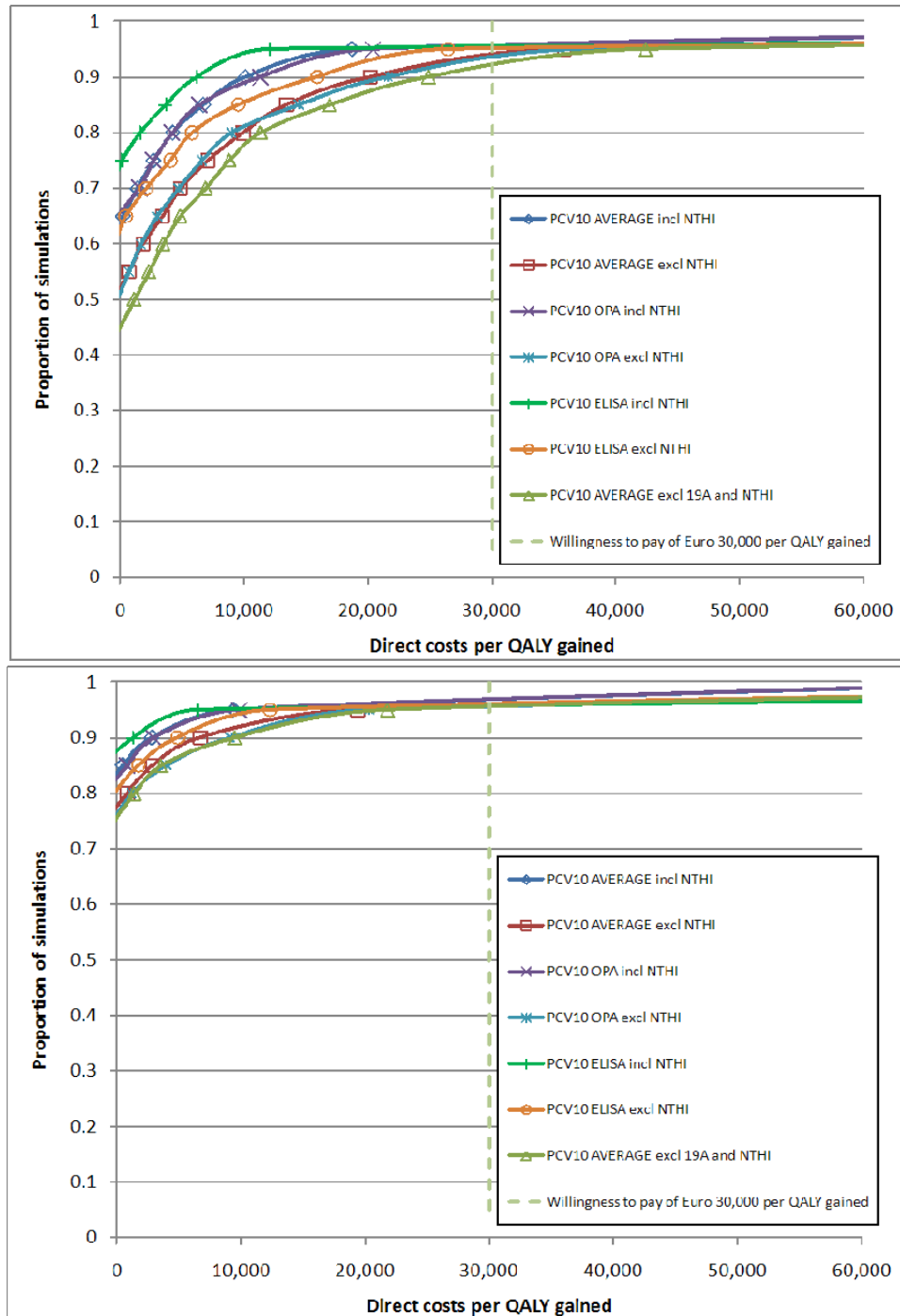
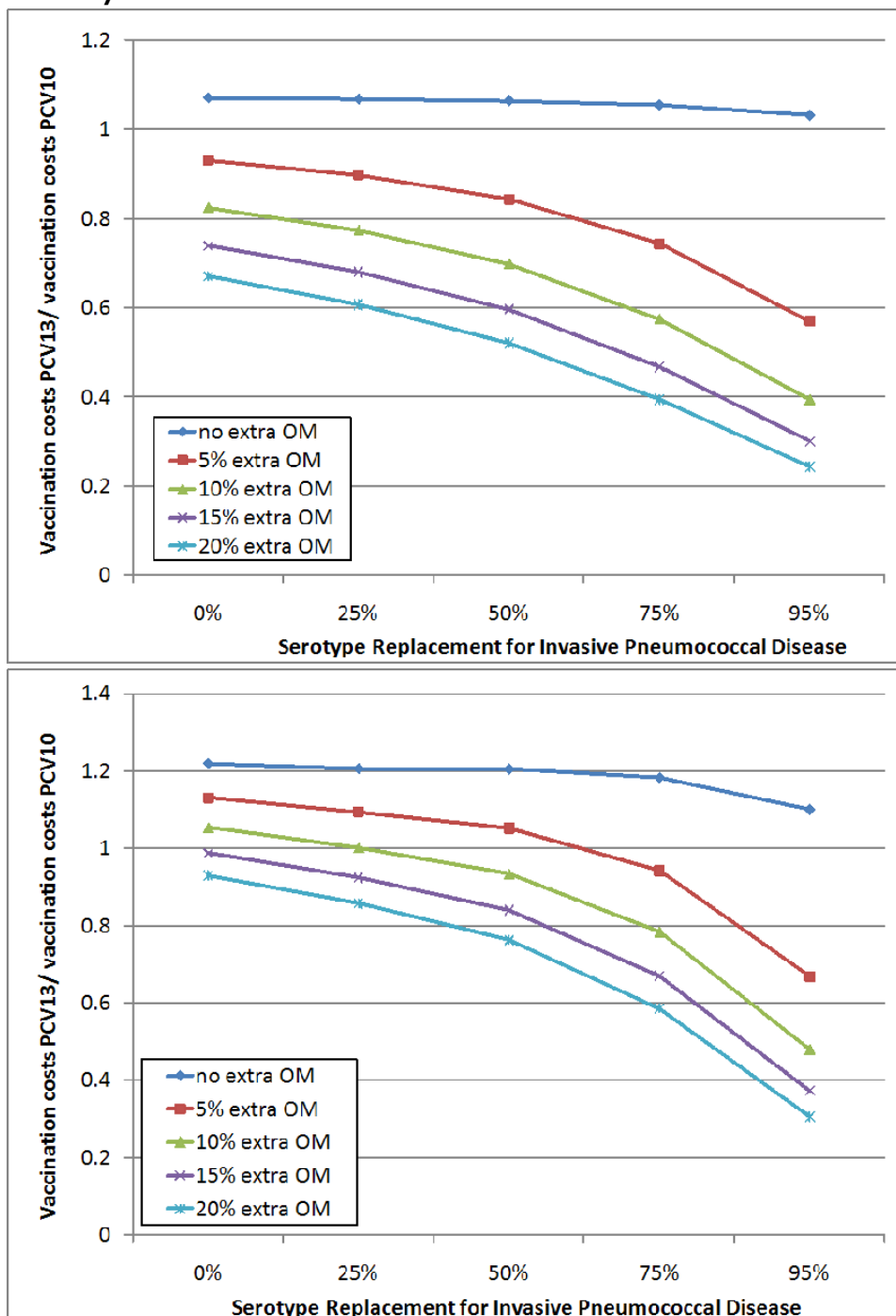


Figure b. Ratio of additional vaccine price per dose of PCV13 versus PCV10 at which both vaccines are equally cost-effective (at €30,000 per QALY gained), for 2+1 schedules, in relation to expected serotype replacement and the additional effectiveness of PCV10 versus PCV13 against otitis media. Upper panel: without herd immunity for IPD; lower panel: with herd immunity for IPD



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