



# The population impact and cost-effectiveness of the 10-valent pneumococcal conjugate vaccine in Iceland

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Thesis for the degree of Philosophiae Doctor

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**Lýðgrunduð áhrif 10-gilda samtengds  
pneumókokka bóluefnis á notkun  
heilbrigðisþjónustu og kostnað**

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## Ágrip

*Streptococcus pneumoniae* er Gram-jákvæð baktería sem getur valdið sýkingum í mönnum. Algengasta birtingarmynd pneumókokka er einkennalaust beraástand í nefkoki. Pneumókokkar eru einnig algengur sjúkdómsvaldur bæði staðbundina og ífarandi sýkinga. Alvarleiki þeirra spannar breitt bil: frá miðeyrnabólgu, sem ganga flestar yfir án inngríps, til blóðsýkinga og heilahimnubólga sem krefjast innlagnar á sjúkrahús. Þrátt fyrir að miðeyrnabólgu séu mildar sýkingar, þá eru þær algengasta orsök læknisheimsókna og sýklalyfjaávísanna barna. Rörísetningar í eyru eru algengustu aðgerðir hjá börnum sem krefjast svæfingar.

Bólusetningar gegn pneumókokkum eiga sér langa sögu. Fyrstu tilraunir í mönnum áttu sér stað 1914. Fjölsykrubóluefni var fyrst þróað árið 1945 en náiði ekki útbreiðslu fyrr en 1983, þegar 23-gilt fjölsykrubóluefni kom á markaðinn. Það vakti hins vegar ekki gott ónæmíssvar í börnum. Til þess þurfti próteintengingu. Sjö-gilt próteintengt pneumókokka bóluefni kom á markaðinn árið 2000. Fjöldi rannsókna hefur sýnt fram á að notkun þess verndi gegn miðeyrnabólgu, rörísetningum, lungnabólgu og ífarandi sýkingum hjá börnum. Einnig hefur verið sýnt fram á hjarðónæmi hjá fullorðnum. Samtengd bóluefni gegn 10 og 13 hjúpgerðum pneumókokka voru framleidd í kjölfarið. Í apríl 2011 var 10-gilda samtengda pneumókokka bóluefnið innleitt í ungbarnabólusetningar á Íslandi.

Markmið bessarar rannsóknar var að meta lýðgrunduð áhrif innleiðingar 10-gilda samtengda pneumókokka bóluefnisins á Íslandi. Sérstök áhersla var lögð á að meta notkun barna á heilbrigðisþjónstu: komur þeirra á heilsugæslu og bráðamóttöku Barnaspítala Hringsins vegna miðeyrnabólgu; sýklalyfjaávísanir og rörísetningar. Einnig voru skoðaðar innlagnir barna á sjúkrahús vegna miðeyrnabólgu, lungnabólgu, blóðsýkinga og heilahimnubólgu. Lýðgrunduð áhrif bólusetningarárinnar voru einnig skoðuð og metið hvort hjarðónæmi hafði myndast hjá fullorðnum. Að lokum var markmið rannsóknarinnar að meta kostnaðarvirkni bóluefnisins á Íslandi.

Einstaklingsgögnum var safnað úr fimm lýðgrunduðum gagnagrunnum og sjúkraskrám Landspítala Háskólasjúkrahúss fyrir tímabilið 1. Janúar 2005 – 31. Desember 2017. Öllum pneumókokkabólusetningum og sýklalyfjaávísunum var safnað úr bólusetningargagnagrunni og lyfjagagnagrunni Embættis Landlæknis. Allar læknisheimsóknir vegna öndunarfærasýkinga voru dregnar úr samskiptaskrá heilsugæslustöðva og sjúkraskrá Landspítala Háskólasjúkrahúss, og upplýsingar um rörísetningar fengust úr endurgreiðslugrunni Sjúkratrygginga Íslands. Upplýsingar um búferlaflutninga barna til og frá Íslandi voru sótt til Hagstofu Íslands.

Fjórar ferilsrannsóknir voru framkvæmdar sem fylgdu eftir fæðingarárgögum 2005-2015. Sú fyrsta fylgdi öllum börnum frá fæðingu til 36 mánaða aldurs

með tilliti til koma á heilsugæslu vegna miðeyrnabólgu. Andersen-Gill líkan var notað sem leiðrétti fyrir aldri, kyni og fjölda fyrri koma vegna miðeyrnabólgu. Áhrif bólusetningarinnar voru metin sem (1 - áhættuhlutfallið milli síðasta bólusetta og óbólusetta árgangsins) \* 100%, sem reyndist vera 22% með 95% öryggisbili 12%-31%. Tíðni ceftriaxone meðferðar við miðeyrnabólgu á Barnaspítala Hringsins var notaður til að áætla áhrif á bóluefnisins á alvarlegar miðeyrnabólgor, og reyndist vera 55% minni í kjölfar bólusetningarinnar með 95% öryggisbili 46%-63%.

Önnur ferilrannsóknin fylgdi börnum eftir til 36 mánaða aldurs með tilliti til allra sýklalyfjaávísanna. Sama líkan var notað og áhrifin metin á sama hátt, og sýklalyfjaávísunum fækkaði um 5.8% með 95% öryggisbili 1.6%-9.8%. Þriðja ferilrannsóknin mat tíðni rörísetninga. Hún fylgdi börnum eftir til 60 mánaða aldurs og sýndi fram á ómarktæka aukningu á rörísetningum, þrátt fyrir innleiðingu bóluefnisins. Fjórða rannsóknin skoðaði sjúkrahúsinnlagnir vegna öndunarfærasykinga. Hún bar saman bólusetta árganga við óbólusetta og sýndi fram á 20% fækkun á innlögnum vegna lungnabólgu, 95% öryggisbil 5%-33%.

Lýðgrunduð rannsókn sem tók til allra aldurshópa mat hjarðónæmi og kostnaðarvirkni bóluefnisins. Rannsókninin beitti aðferðum Bayes á tímaraðgreiningu og notaði komur og innlagnir vegna annarra sjúkdóma til samanburðar. Rannsóknin sýndi fram á sterkt hjarðónæmi sem leiddi til fækkunar á miðeyrnabólgi, lungnabólgi og ífarandi sýkingum. Að teknu tilliti til sparnaðar vegna færri sýkinga, sparaði bóluefnið 7,463,176\$ Bandaríkjadalara á fyrstu fimm árum eftir innleiðingu þess.

Rannsóknirnar sem þessi ritgerð er byggð á sýndu fram á gríðarlegan samfélagslegan ábáta af innleiðingu pneumókokkabóluefnisins á Íslandi. Innleiðingin olli fækkun á læknisheimsóknum, sjúkrahúsinnlögnum og sýklalyfjaávísunum hjá börnum og hjarðónæmi myndaðist hjá fullorðnum. Að teknu tilliti til sparnaðar vegna færri sýkinga sparaði innleiðing bóluefnisins íslenskt samfélag 7,463,176\$ Bandaríkjadalara á föstu 2015 verðlagi.

**Lykilord:** *Streptococcus pneumoniae*, samtengt pneumókokkabóluefni, kostnaðarvirknigreining, hjarðónæmi, miðeyrnabólga

## Abstract

*Streptococcus pneumoniae* is a Gram-positive diplococcus that is both a commensal bacterium in the upper respiratory tract of humans, and a common pathogen. The infectious manifestations of pneumococcus span a range from benign to serious; from acute otitis media (AOM) that often resolves without intervention, to sepsis and meningitis which invariably require hospitalization. Despite its often benign course, AOM is the most common reason for physician visits and antimicrobial prescriptions for children, and tympanostomy tube placements are the most common surgical procedure in children requiring general anesthesia.

Pneumococcal vaccinations have a long history that began in 1914 with clinical trials in humans. A 23-valent polysaccharide vaccine was marketed in 1983 but was poorly immunogenic in children. The seven-valent pneumococcal conjugate vaccine was brought to market in 2000. Multiple studies have demonstrated protection against AOM, tympanostomy tube placements, pneumonia and invasive disease in children. Indirect protection in adults has also been demonstrated. Higher valent vaccines were later developed. In April of 2011, the 10-valent pneumococcal *Haemophilus influenzae* Protein D conjugate vaccine (PHiD-CV10) was introduced in Iceland.

The aim of the study was to evaluate the impact of PHiD-CV10 introduction in Iceland. Special attention was paid to the healthcare burden in children: visits to primary care and to the emergency department of Children's Hospital Iceland for AOM, antimicrobial prescriptions, tympanostomy tube placements, and hospitalizations for pneumonia and invasive disease. The population-based impact of PHiD-CV10 was examined including whether herd effect occurred in adults. Finally, the study aimed to estimate the cost-effectiveness of PHiD-CV10 in Iceland.

Individual level data were obtained from five population-based registries and Landspítali University Hospital's patient registry for the period from 1 January 2005 to 31 December 2017. Data on all administered doses of pneumococcal vaccines and all outpatient antimicrobial prescriptions were extracted from the National Vaccine and National Drug Prescription Registries of the Icelandic Directorate of Health. Visits for respiratory infections were extracted from the Primary Care Registry and Landspítali University Hospital's patient registry, and data on tympanostomy procedures were obtained from Icelandic Health Insurance's reimbursement database. Immigration and emigration data were provided by Statistics Iceland.

Four cohort studies followed 11 Icelandic birth-cohorts 2005-2015. The first such study followed children from birth to 36 months of age with regards to primary care visits for AOM. An Andersen-Gill model that corrected for age,

gender and the number of previous AOM visits was used. The vaccine impact was calculated as (1 - hazard ratio between the last vaccine eligible and vaccine non-eligible cohort) \* 100%, and revealed a 22% reduction in AOM with a 95% confidence interval (CI) 12% to 31%. The incidence of ceftriaxone treated AOM at Children's Hospital Iceland was examined before and after vaccine introduction to estimate the vaccine impact on AOM with treatment failure, and revealed a 55% (95% CI 46%-63%) reduction in ceftriaxone treatment episodes.

The second cohort study followed children from birth to 36 months of age with regards to outpatient antimicrobial prescriptions. The same methods were used, and the vaccine impact was calculated. A 5.8% (95% CI 1.6%-9.8%) decrease in the number of prescriptions was established. The third cohort study evaluated tympanostomy procedures. It followed children from birth to 60 months of age and revealed a non-significant increase in procedures, despite the introduction of PHiD-CV10. The fourth cohort study examined the hazard of hospitalization for respiratory and invasive infections. It compared vaccine eligible cohorts to vaccine non-eligible cohorts and found a 20% (95% CI 5%-33%) reduction in pneumonia hospitalizations.

A population-based study that included all age-groups estimated the cost-effectiveness of PHiD-CV10 and examined whether herd effect had occurred. A Bayesian time series methodology was used and included visits and hospitalization for diagnoses unrelated to the vaccine as controls. The study revealed strong evidence of herd effect for otitis media, pneumonia and invasive disease. After taking into account costs avoided because of prevented disease cases, the introduction of PHiD-CV10 was found to have saved 7,463,176 United States Dollars in the first five years of the program.

The studies that compromise this thesis showed a large societal impact of PHiD-CV10 introduction; visits, antimicrobial prescriptions and hospitalizations of children decreased, and indirect protection was observed in adults. The vaccination program was cost-saving from both the health sector and societal perspectives.

**Keywords:** *Streptococcus pneumoniae*, Pneumococcal conjugate vaccines, cost-effectiveness analysis, otitis media, herd immunity

## Acknowledgements

My son was born in June of 2013. During the past five years, he has learned to walk, talk, laugh, sing, dance, tell jokes and make friends – a strong foundation upon which to build his future as a happy and productive member of society. He didn't achieve this on his own. He was nurtured taught by his family and by his wonderful pre-school teachers. In November of 2013, the University of Iceland Faculty of Medicine accepted my application for doctoral studies. I had no prior experience in scientific research, nor had I written any English text. During the same five-year period in which my son learned to be a human, I learned to be researcher; granted, a slightly less impressive accomplishment. I too did not achieve this by myself. I would like to acknowledge those who contributed to my training.

First, I thank my supervisor, Professor, Chief and Faculty Chairman of Pediatrics, Dr. Ásgeir Haraldsson. He, along with other members of my doctoral committee, created the environment and conditions required for me to become a researcher. He provided excellent mentorship, while pushing me to be independent. Our first interaction was in April of 2013, when in a phone call, he introduced himself and promptly offered me a PhD position. I had recently completed a small cost-effectiveness analysis for my Bachelor of Science in Medicine, supervised by Professor of Economics Dr. Tinna Laufey Ásgeirsdóttir – Ásgeir's daughter. I can only surmise that she saw in me some inkling of potential and recommended me for doctoral studies. She would later represent a fifth of my doctoral committee and instruct me in the methodology of health economic analysis. I thank her for her help during the past five years.

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support regarding the problem at hand. The meetings were of immeasurable value, and as I later learned, above and beyond what is expected of a doctoral committee.

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## List of abbreviations

Term	Abbreviation
Acute otitis media	AOM
Anatomical-Therapeutic-Chemical	ATC
Community-acquired pneumonia	CAP
Cost-benefit analysis	CBA
Cost-effectiveness analysis	CEA
Cost-effectiveness acceptability curve	CEAC
Case-fatality ratio	CFR
Confidence intervals	CI
Cost-utility analysis	CUA
Enzyme-linked immunosorbent assay	ELISA
Hospital-acquired pneumonia	HAP
Hazard ratio	HR
International Classification of Diseases, 10th revision	ICD-10
Intensive care unit	ICU
Invasive pneumococcal disease	IPD
Incidence rate	IR
Incidence rate ratio	IRR
Icelandic krona	ISK
International Society for Pharmacoeconomics and Outcome Research	ISPOR
Leave-one-out cross-validation	LOOCV
Lower respiratory tract infection	LRTI
Meningococcal outer membrane protein complex	MOMP
NOMESCO Classification of Surgical Procedures	NCSP
National Drug Prescription Registry	NDPR
non-typeable <i>Haemophilus influenzae</i>	NTHi
National Vaccine Registry	NVR

Organization for Economic Co-operation and Development	OECD
Principal component analysis	PCA
Pneumococcal conjugate vaccine	PCV
10-valent pneumococcal conjugate vaccine	PCV10
11-valent pneumococcal conjugate vaccine	PCV11
13-valent pneumococcal conjugate vaccine	PCV13
7-valent pneumococcal conjugate vaccine	PCV7
10-valent pneumococcal <i>Haemophilus influenzae</i> protein-D conjugate vaccine	PHiD-CV10
23-valent pneumococcal polysaccharide vaccine	PPV-23
Probabilistic sensitivity analysis	PSA
Quality-adjusted life-years	QALY
Respiratory syncytial virus	RSV
Seasonal and trend decomposition using LOESS	STL
Tympanostomy tube placement	TTP
Upper respiratory tract infection	URTI
Vaccine eligible cohorts	VEC
Vaccine non-eligible cohorts	VNEC

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## List of Original Papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-VI):

- I. Eythorsson E, Hrafnkelsson B, Erlendsdóttir H, Atli Gudmundsson S, Kristinsson KG, Haraldsson Á. Decreased AOM with Treatment Failure Following Introduction of the Ten-Valent Pneumococcal Haemophilus influenzae Protein D Conjugate Vaccine. *Pediatr Infect Dis J.* December 2017;1: doi:10.1097/INF.0000000000001870.
- II. Sigurdsson S, Eythorsson E, Hrafnkelsson B, Erlendsdóttir H, Kristinsson KG, Haraldsson Á. Reduction in All-Cause Acute Otitis Media in Children <3 Years of Age in Primary Care Following Vaccination With 10-Valent Pneumococcal Haemophilus influenzae Protein-D Conjugate Vaccine: A Whole-Population Study. *Clin Infect Dis.* 2018;67(8):12131219. doi:10.1093/cid/ciy233.
- III. Eythorsson E, Sigurdsson S, Hrafnkelsson B, Erlendsdóttir H, Haraldsson Á, Kristinsson KG. Impact of the 10-valent pneumococcal conjugate vaccine on antimicrobial prescriptions in young children: a whole population study. *BMC Infect Dis.* 2018;18(1):505. doi:10.1186/s12879-018-3416-y.
- IV. Eythorsson E, Sigurdsson S, Erlendsdóttir H, Hrafnkelsson B, Kristinsson KG, Haraldsson Á. Increase in tympanostomy tube placements despite pneumococcal vaccination, a population-based study. *Acta Paediatr.* January 2019;1-8. doi:10.1111/apa.14724.
- V. Sigurdsson S, Eythorsson E, Erlendsdóttir H, Hrafnkelsson B, Kristinsson KG, Haraldsson Á. Impact of the 10-valent pneumococcal conjugate vaccine on hospital admissions in children under three years of age in Iceland (Submitted for publication in *Vaccine*)
- VI. Eythorsson E, Hrafnkelsson B, Erlendsdóttir H, Kristinsson KG, Haraldsson Á. Impact and cost-effectiveness of the 10-valent pneumococcal conjugate vaccine in Iceland, a population-based study (Submitted for publication in *BMJ*)

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## **Declaration of contribution**

- Paper I. The doctoral student, Elias Eyþórsson (EE), collected the data, refined the research question and conceptualized the study design under the guidance of Ásgeir Haraldsson (ÁH), Helga Erlendsdóttir (HE) and Karl G. Kristinsson (KGK). EE did the statistical analysis under the supervision of Birgir Hrafnkelsson (BH). EE drafted the paper and revised it alongside his co-authors.
- Paper II. EE collected and structured the data. EE refined the research question and conceptualized the study design along with Samúel Sigurðsson (SS), ÁH, HE, and KGK. EE analyzed the data and did the statistical analysis with oversight by BH. EE and SS drafted and revised the paper, and did critical revisions alongside their co-authors.
- Paper III. EE collected and structured the data. EE refined the research question and conceptualized the study design along with ÁH, HE, KGK, and SS. EE analyzed the data and did the statistical analysis, which was reviewed by BH. EE and SS drafted and revised the paper, and EE did critical revisions alongside his co-authors.
- Paper IV. EE collected and structured the data. EE refined the research question and conceptualized the study design along with ÁH, HE, KGK, and SS. EE analyzed the data and did the statistical analysis, which was reviewed by BH. EE and SS drafted the paper, and EE did critical revisions alongside his co-authors.
- Paper V. EE collected and structured the data. EE and SS refined the research question and conceptualized the study design along ÁH, HE, and KGK. EE analyzed the data and did the statistical analysis, which was reviewed by BH. EE and SS drafted and revised the paper, and did critical revisions alongside their co-authors
- Paper VI. EE collected and structured the data. EE refined the research question and conceptualized the study design along with Tinna Laufey Ásgeirs Þóttir (TLÁ), ÁH, HE, and KGK. EE analyzed the data and did the statistical analysis, which was reviewed by BH. EE drafted and revised the paper, and did critical revisions alongside his co-authors.
- EE wrote the thesis under guidance from his doctoral committee.



## 1 Introduction

*Streptococcus pneumoniae* is a commensal bacterium found in the nasopharynx of humans (Hussain et al. 2005). It is also a common pathogen, and one of the most common bacterial causes of lower respiratory disease in humans (K. L. O'Brien et al. 2009; Troeger et al. 2018). In classical medical texts, pneumococcus is described as a Gram-positive lancet-shaped coccus, usually found in pairs. In fact, pneumococcus is *the* Gram-positive coccus, being the first bacteria noted by the Danish scientist Christian Gram that retained the dark aniline-gentian violet stain that now bears his name (Gram 1884). Pneumococcus was first isolated in 1881 by two microbiologists, George M. Sternberg in the United States and Louis Pasteur in France (Pasteur 1881; Sternberg 1882; Watson et al. 1993). The causal association between this newly discovered bacterium and pneumonia was firmly established only five years later (Weichselbaum 1886), and in the following decade, all clinical presentations of pneumococcal infections had been described (Austrian 1981).

Pneumococcus has gone by many names since it was first isolated in 1881. It was originally named *Micrococcus pasteurii* by Sternberg (Sternberg 1882), but by 1920, a scientific consensus was reached that the official name should be *Diplococcus pneumoniae* (Winslow et al. 1920). It was not until 1974 that pneumococcus received its current name, *Streptococcus pneumoniae* (Deibel and Seeley 1974).

The infectious manifestations of pneumococcal disease are, broadly speaking, local infections of the respiratory tract and infections of previously sterile tissue. They range from common to uncommon, and from benign to serious. The most common infectious manifestation of pneumococcus is acute otitis media (AOM) – an infection of the middle ear (Coker et al. 2010; Ngo et al. 2016). The disease course is benign and rarely results in permanent disability (Vergison et al. 2010). On the other hand, AOM is the most common reason for physician visit and for antimicrobial prescription in the pediatric population (Grijalva, Nuorti, and Griffin 2009; Todberg et al. 2014). Antimicrobial consumption is causally related to antimicrobial resistance, a major threat to public health (Arason et al. 1996; Austin, Kristinsson, and Anderson 1999). Recurrent or persistent otitis media is sometimes treated with the surgical placement of tympanic tubes, rendering it

the most common surgical procedure requiring general anesthesia in children (Cullen, Hall, and Golosinskiy 2009). Thus, while AOM is a benign disease, it is associated with a large health care burden (Arguedas et al. 2010; Monasta et al. 2012).

A potentially more serious manifestation of pneumococcal disease is pneumonia, the disease from which pneumococcus gets its name. Pneumonia often requires hospitalization and intravenous antimicrobial treatment, and can lead to permanent disability and death (Troeger et al. 2017). Pneumococcus can cause invasive infections if it gains access to normally sterile tissue. These includes bacteremia, an infection of the blood, and meningitis, an infection of the meninges. These infectious manifestations are grouped together as invasive pneumococcal disease (IPD). Whilst IPD is uncommon, the consequences can be disastrous (Feikin et al. 2000; Ricketson et al. 2013; Tsigrelis et al. 2008). The case-fatality ratio (CFR) from pneumococcal meningitis in Icelandic children and adults is estimated at 13% and 8% respectively (Snaebjarnardóttir et al. 2013; Þórðardóttir et al. 2014). Pneumococcal infections are responsible for a large health care burden that spans the range from outpatient to inpatient treatment (Backhaus et al. 2016; Pulido and Sorvillo 2010).

For over a century, scientists have attempted to prevent pneumococcal disease using vaccines with varying results. Pneumococcal vaccine development is complicated by the polysaccharide coating that protects pneumococcus from environmental factors. The polysaccharide capsule acts as an “invisibility cloak” to the human immune system, rendering it unable to detect pneumococcus except through defined patterns in the oligosaccharides contained within the capsule (Tuomanen, Austrian, and Masure 1995). Pneumococcus has been classified into over 97 different serotypes to date based on the polysaccharide capsule (Habib, Porter, and Satzke 2014). As the capsule contains only polysaccharides and not proteins, the immune response is T-cell independent and therefore poorly immunogenic, especially in children, even after being identified by the immune system (Geno et al. 2015).

The epidemiology of pneumococcus is dominated by person-to-person transmission of asymptomatic carriage (Beutels et al. 2006). Because young children do not have previous immunity to any serotype, they are colonized by pneumococcus more frequently, and each colonization lasts longer (Melegaro, Gay, and Medley 2004). This phenomenon is further augmented when multiple immune-naïve children congregate, such as in daycare centers

and pre-schools (Yagupsky et al. 1998). Thus, children act as a pneumococcal reservoir for the population, often without having any clinical disease (Hoshino et al. 2002; Le Polain de Waroux et al. 2014; Mosser et al. 2014; Quirk et al. 2018). Vaccinating children against certain serotypes may therefore lead to a decrease in pneumococcal disease caused by those serotypes in adults. In vaccine epidemiology, this is referred to as herd-effect and is an important consideration for pneumococcal vaccine development (Halloran, Longini, and Struchiner 2010; Tsaban and Ben-Shimol 2017). Serotype replacement can also occur, where previously rare serotypes appear and fill the ecological niche vacated by the vaccine serotypes (Weinberger, Malley, and Lipsitch 2011; Quirk et al. 2018).

Health systems operate under constraints on budgets and resources. Demonstrating vaccine benefit for individuals is essential, but not the only factor to consider when making health policy decisions. Cost and resource allocation are also of great importance. The diseases prevented by an intervention have associated expenses which must be accounted for when the expenditures for the intervention are evaluated. This is especially complicated in the case of vaccines, because benefits are not seen immediately but rather over time and occur in both vaccinated and unvaccinated members of the population (Isaacman et al. 2008; Kim and Goldie 2008). Cost-effectiveness analysis and cost-benefit analysis are methods developed to measure the ratio between expenditure and benefit, and are used as a tool in making health policy decisions (Gray et al. 2011). To adequately perform such analyses, detailed data on disease incidence and associated costs for the whole population must be available.

Iceland is an independent island nation, isolated in the mid-Atlantic, with a relatively homogeneous population of roughly 350,000 individuals. The first systematic program of vaccination against pneumococcus in Iceland began in April 2011, when the 10-valent pneumococcal *Haemophilus influenzae* protein-D conjugate vaccine (Synflorix, PHiD-CV10) was introduced into the national pediatric vaccination program. The vaccine program entailed two primary doses given at three and five months of age, and a booster dose at 12 months. No catch-up program was undertaken. Prior to the introduction, no systematic vaccination effort had been undertaken in Iceland.

As the other Nordic countries, Iceland has a rich legacy of national health-related registers. Detailed individual-level information on vaccine status, outpatient primary care visits, antimicrobial consumption, tympanic tube procedures and hospitalizations are accessible, and can be linked between

the registries using national identification numbers. All health care costs are available on the individual-level from Icelandic Health Insurance, which is the insurer of all permanent Icelandic residents. This wealth of medical documentation enabled a unique whole-population ecological study examining the impact of systematic pneumococcal vaccination.

## **1.1 Clinical manifestations of *Streptococcus pneumoniae***

In this chapter the clinical manifestations of pneumococcal disease will be reviewed. The mechanism by which individuals acquire pneumococcus into their normal upper respiratory flora will be discussed, and the association between pneumococcal carriage and disease will be described. Throughout this thesis, attention will be focused on three common clinical presentations of pneumococcal infections; otitis media, pneumonia and invasive pneumococcal disease, including the pathophysiology, natural disease course, and health care burden of each of the presentations.

Because pneumococcus is both a commensal bacterium and a pathogen, its relationship with humans is complex. Most children are colonized by pneumococci within the first months of life (Leino et al. 2001). Over the course of their lifetime, a child will be colonized by many different serotypes (Hussain et al. 2005; Le Polain de Waroux et al. 2014). Their immune system will learn to recognize newly acquired serotypes, and will either clear the colonization or maintain an equilibrium in which the serotype is kept within a certain limit of reproduction (Dowling, Sheehe, and Feldman 1971; Melegaro, Gay, and Medley 2004). In this manner, the contribution of pneumococcus to the human upper respiratory flora is in a state of constant flux (Devine et al. 2015). New serotypes enter and are carried for a variable period of time, and the relative density of serotypes changes (Rodrigues et al. 2016; Thors et al. 2018).

In some cases, the equilibrium between pneumococci and the host is destabilized resulting in clinical manifestations (Bergenfelz and Hakansson 2017). It is thought that this is most likely to occur directly following the acquisition of new serotype into the nasopharyngeal flora, though it may occur at any time (Casey, Adlowitz, and Pichichero 2009). Because pneumococcus is carried in the nasopharynx, this disequilibrium results in infections of adjacent tissue; the sinuses, middle ear and conjunctiva (Syrjänen et al. 2005). The pathogenesis of pneumococcal pneumonia is thought to occur through micro-aspiration of upper respiratory secretions,

provoking a subsequent rapid proliferation of pneumococcus in the lower respiratory tract (Cilloniz et al. 2016).

Invasive disease occurs when pneumococcus penetrates the host's immunological defenses and proliferates in normally sterile tissue (Song, Nahm, and Moseley 2013). This can occur as a primary event, or can be secondary to infections of the upper or lower respiratory tract. Generally, IPD is considered to encompass bacteremic pneumonia, empyema, septicemia and meningitis (Song, Nahm, and Moseley 2013). While some may argue that the middle ear is normally sterile, AOM is not considered invasive disease.

### **1.1.1 Acute otitis media**

Otitis media is an inflammatory state of the middle ear that is most often caused by a viral or bacterial infection (Bergenfelz and Hakansson 2017; Heikkinen and Chonmaitree 2003). The clinical presentation of otitis media is variable. Its onset ranges from abrupt to gradual, and its duration from short to protracted (Thornton et al. 2011). Several categories have been defined to facilitate communication concerning this variability. They are not mutually exclusive, but rather represent a continuum of the disease process. Otitis media can manifest as an acute inflammatory event. This is the classical acute otitis media with which most parents are familiar. AOM can be recurrent, which is defined as AOM occurring three times over a six month period, or four or more times over a 12 month period (Pichichero et al. 2008; Venekamp et al. 2018). Conversely, it can take the form of a chronic low-grade process. The later phenotype includes otitis media with effusion and chronic suppurative otitis media (Chen et al. 2013; Rosenfeld et al. 2016)

#### **1.1.1.1 Pathogens implicated in acute otitis media**

Any pathogen that is able to gain access to the middle ear, disrupt the normal function of the Eustachian tube and replicate within the resulting fluid, has the potential to cause otitis media. Though most studies focus on bacterial pathogens, the most common cause of AOM is Eustachian tube dysfunction caused by viral infection (Heikkinen and Chonmaitree 2003). Even when bacteria are cultured from middle ear fluid of children experiencing AOM, the causative agent may still be a virus, and the bacteria an innocent bystander that was trapped in the middle ear following acute closure of the Eustachian tube (Chonmaitree et al. 2016). In upwards of 90% of otitis media cases with a positive bacterial culture, the bacteria aspirated from the middle ear fluid will also be found in the nasopharynx (Casey, Adlowitz, and Pichichero

2009). The most common bacterial causes of otitis media are *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae* (NTHi), and *Moraxella catarrhalis* (Bluestone, Stephenson, and Martin 1992; Casey and Pichichero 2004; Casey, Adlowitz, and Pichichero 2009; Ngo et al. 2016; Pumarola et al. 2013). The relative contribution of these three pathogens is remarkably stable between countries and over time (Ngo et al. 2016). This is likely a consequence of how common they are in the nasopharyngeal flora of children.

A systematic review of studies from 1970-2014 which reported the etiology of otitis media, found that *Streptococcus pneumoniae* caused 30% of acute otitis media in Europe (Ngo et al. 2016). In countries that have introduced systematic pneumococcal vaccination, there is evidence to suggest that the microbiology of otitis media has shifted from being predominantly due to pneumococcus to predominantly due to NTHi (Block et al. 2004; Van Dyke et al. 2017). Of the pneumococcal AOM, the prevalence of vaccine serotypes has decreased, and non-vaccine serotypes now predominate. Children with otitis media who experience spontaneous rupture of the tympanic membrane have a slightly different distribution of pathogens, with a higher proportion of *Streptococcus pyogenes* and *Staphylococcus aureus* (Chen et al. 2013; Quirk et al. 2018; Sonsuwan, Watcharinyanon, and Sawanyawisuth 2016). This could be explained by these pathogens causing a more aggressive infection, or possibly by contamination by bacteria located in the external ear canal. Similarly, coagulase negative staphylococci and *Staphylococcus aureus* are more common in otitis media with effusion (Kim et al. 2013).

#### **1.1.1.2 Health care burden of otitis media**

The health care burden caused by otitis media is disproportionate to the severity of the disease (Ahmed, Shapiro, and Bhattacharyya 2014). Acute otitis media is the most common reason for physician visit among children, a fact which has been frequently documented in multiple countries (Arguedas et al. 2010; Marchisio et al. 2012; Monasta et al. 2012). Only focusing on physician visits underestimates the impact of AOM, as some episodes are not reported to physicians but still result in distressing symptoms in children and parental missed days of work (Blank et al. 2014). A Dutch study which surveyed parents of children younger than one year of age repeatedly for 12 consecutive months found that the incidence of parentally reported acute otitis media episodes was 624 per 1,000 person-years, and that only half resulted in physician visits (Fortanier et al. 2015). By a child's third birthday,

60% to 80% will have experienced at least one episode of AOM (Kaur, Morris, and Pichichero 2017; Teele, Klein, and Rosner 1989). The incidence of outpatient AOM in children is reviewed in Table 1.

Table 1. A review of observed incidence rates of acute otitis media in high-income countries prior to the introduction of pediatric pneumococcal conjugate vaccination. Countries are displayed in alphabetical order. The studies report incidence for different age-groups. The incidence is provided per 100 person-years. When applicable, the cumulative incidence of children who had experienced at least one episode of otitis media by a certain age are displayed. Only two studies were designed to capture this measure of incidence. Only Sigurdsson et al. (2018) provided information on both incidence and cumulative incidence. Missing information is indicated with a hyphen (-).

Study	Country	Observation year	Age (years)	Incidence (per 100 person-years)	Cumulative incidence
De Wals et al. (2009)	Canada	2000	0-5	59	-
Todberg et al. (2014)	Denmark	2010	0-7	-	60% by seven
Usonis et al. (2016)	Estonia	2013	0-5	14	-
Adam and Fehnle (2008)	Germany	2007	0-2	29	-
Liese et al. (2014)	Germany	2010	0-5	26	-
Gudnason et al. (2012)	Iceland	2000	2-6	68	-
Sigurdsson et al. (2018)	Iceland	2005-2010	0-3	44	60% by three
Esposito et al. (2007)	Italy	2002	0-2.5	47	-
Marchisio et al. (2012)	Italy	2004	0-6	16	-
Liese et al. (2014)	Italy	2010	0-5	20	-

Usonis et al. (2016)	Lithuania	2013	0-5	18	-
Gribben et al. (2012)	New Zealand	2009	0-4	27	-
Usonis et al. (2016)	Poland	2013	0-5	12	-
Usonis et al. (2016)	Romania	2013	0-5	14	-
Usonis et al. (2016)	Slovenia	2013	0-5	34	-
Liese et al. (2014)	Spain	2010	0-5	33	-
Gisselsson- Solen (2017)	Sweden	2009	0-4	47	-
Liese et al. (2014)	Sweden	2010	0-5	26	-
Lau et al. (2015)	United Kingdom	2005	0-10	13	-
Liese et al. (2014)	United Kingdom	2010	0-5	23	-
Grijalva, Nuorti, and Griffin (2009)	United States	1996	0-5	95	-
Grijalva et al. (2006)	United States	1999	0-2	142	-
Zhou et al. (2008)	United States	1999	0-2	207	-
Poehling (2004)	United States	2000	0-2	178-225	-

Likewise, otitis media is also responsible for the majority of antimicrobial prescriptions, and thus contributes significantly to antimicrobial resistance (Austin, Kristinsson, and Anderson 1999; Grijalva, Nuorti, and Griffin 2009). Though often benign and self-limiting, AOM can progress to recurrent or chronic infection and require more invasive treatment (Cullen, Hall, and Golosinskiy 2009; Vlastarakos et al. 2007). Mastoiditis is a rare but serious

complication of AOM that invariably requires hospital admission and administration of intravenous antimicrobials (Finnbogadóttir et al. 2009; Groth et al. 2011).

### **1.1.1.3 Tympanostomy tube procedures**

For various reasons, parents and clinicians may opt to treat recurrent or chronic otitis media with the placement of a tympanic tube. Tympanic tube procedures are consequently the most common surgical procedure requiring general anesthesia in the pediatric population (Black 1984; Cullen, Hall, and Golosinskiy 2009). Despite their popularity, there is little evidence for the use of tympanostomy tubes for their two most common indications; recurrent otitis media and hearing loss associated with otitis media with effusion (Browning et al. 2010; Paradise et al. 2001, 2007; Venekamp et al. 2018). Inconsistent evidence regarding the efficacy of tympanostomy tube procedures is mirrored in the large variation in incidence that is seen both within and between different countries (Table 2).

Table 2. A review of observed incidence rates of tympanostomy tube placements in high-income countries prior to the introduction of pediatric pneumococcal conjugate vaccination. Countries are displayed in alphabetical order. The studies report incidence for different age-groups. The incidence is provided per 100 person-years. When applicable, the cumulative incidence of children who had undergone at least one procedure by a certain age are displayed. Missing information is indicated with a hyphen (-)

Study	Country	Observation year	Age (years)	Incidence (per 100 person-years)	Cumulative incidence
Spilsbury et al. (2006)	Australia	2005	0-14	6	8% by 15
Falster et al. (2013)	Australia	2007	0-8	6	4% by eight
Coyte et al. (2001)	Canada	1999	0-14	8	-
Desai, Kellner, and Drummond (2002)	Canada	2000	0-15	11	7% by three
Howitz et al. (2017)	Denmark	2007	0-15	38	-

Djurhuus et al. (2014)	Denmark	2007	0-15	32	29% by five
Groth, Thomsen, and Ovesen (2015)	Denmark	2007	0-2	76	1% by 10
Pedersen et al. (2016)	Denmark	2007	0-3	101	24% by three
Haapkylä et al. (2008)	Finland	2005	0-7	15	-
Sarasoja et al. (2013)	Finland	2008	2-13	-	15% by 13
Palmu et al. (2017)	Finland	2009	0-5	5	-
A. Palmu et al. (2015)	Finland	2010	0-2	8	13% by two
Arason et al. (2002)	Iceland	1998	0-5	-	30% by six
Arason et al. (2005)	Iceland	2003	0-5	-	34% by six
Kvaerner, Nafstad, and Jaakkola (2002)	Norway	1996	0-4	-	9% by five
Haapkylä et al. (2008)	Norway	2005	0-7	12	-
Florentzson and Finizia (2012)	Sweden	2006	0-10	-	-
Gisselsson-Solen (2017)	Sweden	2007	0-4	8	-
Black (1984)	United Kingdom	1982	0-9	9	-
Bright et al. (1993)	United States	1988	0-17	-	13% by 18

Kogan et al. (2000)	United States	1991	0-3	-	7% by three
Cullen, Hall, and Golosinskiy (2009)	United States	2006	0-14	11	-

The variation can possibly be explained by different thresholds for performing the procedure. By carefully examining the medical records of all children who underwent tympanic tube procedures in five hospitals in New York, Keyhani et al. were able to show that 92% of the procedures would not have been recommended according to the guidelines in force at the time of surgery (Keyhani et al. 2008).

#### **1.1.1.4 Acute otitis media in Iceland**

The incidence AOM, its microbiology, treatment and complications have been evaluated in Iceland. In 1990, a retrospective analysis of two birth-cohorts in a small village in Iceland showed a 66% cumulative incidence of AOM by 24 months of age (Bjarnason, Friðriksson, and Benediktsson 1991). A larger study conducted in 1998 used parental questionnaires to estimate the incidence of upper respiratory infections that resulted in antimicrobial treatment and tympanic tube placements among children ages one to six years old (Arason et al. 2002). A total of 1030 children were randomly sampled from four geographically separated areas of Iceland and the study achieved a 78% response rate. The study demonstrated high incidence rates of antimicrobial treated AOM for all age-groups, ranging from 1.79 treatment episodes among children one year of age to 0.25 treatment episodes in children six years of age. In this random sample, 58% of all antimicrobial prescriptions were due to AOM. The cumulative incidence of tympanic tube placements was alarmingly high. By one year of age, 23% (95%CI 16%-31%) had already received at least one tympanostomy tube. This proportion exceeded 30% by age two and remained fairly stable thereafter. The study was repeated by the same investigators in 2003 using the exact same cross-sectional random sampling (Arason et al. 2005). The proportion of all antimicrobial prescriptions that were due to AOM was almost exactly the same, 57%. Surprisingly, the cumulative incidence of tympanostomy tube placement had slightly increased and was now estimated to be 34%, A study evaluating a hygiene intervention in daycare centers in the capital region in Iceland using parental questionnaires reported the rate of AOM to be 67 per

100 person-years among children two to six years of age from 2000 to 2001 (Gudnason et al. 2012).

### **1.1.2 Pneumonia**

Pneumonia is defined as the infectious infiltration of the lung parenchyma. It is classified as community acquired pneumonia if it is detected in people with limited contact with the health care system in the weeks prior to diagnosis. Remaining pneumonia cases are classified as health care associated pneumonia, or hospital-acquired pneumonia if diagnosed during a hospital admission. This simple classification system is remarkably good at predicting antimicrobial resistance in the causative pathogen, and informs the choice of antimicrobial agents (Mackenzie 2016).

#### **1.1.2.1 *Pathogens causing pneumonia***

Any pathogen that can gain access to the lung and replicate there, has the potential to cause pneumonia. As is the case of otitis media, the most common bacterial pathogens causing community acquired pneumonia in children are *Streptococcus pneumoniae* and *Haemophilus influenzae* (Rodrigues and Groves 2017). Here again, this is most likely to be a function of how common these pathogens are in the upper respiratory flora. In the case of pneumonia, it is exceedingly difficult to determine the causative pathogen (Cilloniz et al. 2016; Feikin et al. 2017). Ideally, a sample would be taken from the lung itself, but the dangers of such procedures render this option unfeasible. Most studies, therefore, use proxy measures such as sputum, blood cultures and nasopharyngeal swabs. In addition, the inability of children to produce a quality sputum sample exacerbates the difficulties of determine the causative pathogen in this age group (Rodrigues and Groves 2017).

The relative contribution of pathogens varies greatly with the age and risk factor profile. Only a few studies in developed countries have evaluated the distribution of pathogens which cause pneumonia in children, but they have consistently demonstrated the importance of viruses in pediatric pneumonia (Berg et al. 2016; Jain et al. 2015; Rudan et al. 2013). Results have either indicated that viruses are the primary etiological factor, or that viruses weaken the respiratory defenses and allow bacterial disease to develop (Feikin et al. 2017). The considerable heterogeneity in the proportion of pneumonias found to be caused by various pathogens, underscores the importance of study population, time-period and, most importantly, the methods used in determining the causative pathogen (Feikin et al. 2017). A

large multicenter study, The Pneumonia Etiology Research for Child Health (PERCH), is underway to clarify the etiology of pediatric pneumonia (Levine et al. 2012). Its results have not yet been published.

One of the first prospective studies of pediatric pneumonia was undertaken in Chapel Hill, North Carolina, from 1963 to 1971. The study investigated all lower respiratory infections in children, and found most to be caused by respiratory syncytial virus (RSV), parainfluenza virus and *Mycoplasma pneumoniae* (Glezen and Denny 1973). The predominance of causative viruses is likely due to the methods, current at the time, used to detect etiology. Following the advent of pneumococcal antibody testing, the recognition of pneumococcus as an important pathogen increased. Using pneumococcal antigens, Paisley et al. (1984) found pneumococcus to be a contributor in 19% of pediatric pneumonias from 1978-1979. In a study conducted in Göteborg, Sweden from 1982-1983, a primitive enzyme-linked immunosorbent assay was used to determine etiology, and found that 13% of pediatric pneumonias were due to *Streptococcus pneumoniae* (Claesson et al. 1989). In that study, however, antibody testing for pneumococcus was only performed on those who were found to be pneumococcal carriers by nasopharyngeal swap. A few years later, in 1989, a prospective study of pediatric pneumonia in Turku, Finland demonstrated pneumococcus to be a causative pathogen in 38% of cases (Ruuskanen et al. 1992). Another etiological study in Paris in 1992-1994, enrolled 104 consecutive children who presented with pneumonia to a single hospital. Of those, 14% were found to have pneumococcal pneumonia (Gendrel et al. 1997).

In populations where pneumococcal vaccination is universal, two studies on the etiology of pediatric pneumonia have been published. One of these, conducted in the United Kingdom in 2009-2011, found pneumococcus to be causative in 17.4% of cases (Elemraid et al. 2013). The other is a large prospective study of 2,358 children conducted in 2011-2012 in the United States, which utilized a variety of sampling methods, and detected pneumococcus in only 4% of cases, a result considerably different than all other etiological studies of pediatric pneumonia (Jain et al. 2015). The authors' discussion of possible reasons for this included speculation that low proportion of pneumococcal pneumonia might be due to universal pneumococcal vaccination.

All of the above studies identified respiratory syncytial virus to be the most common causative pathogen. Of the bacterial pneumonias, all but one found pneumococcus to be the most common. Their interpretation is complicated

by the lack of direct sampling from the lungs. In studies that used strict radiological inclusion criteria and lung aspiration to determine the etiology, pneumococcus was found to cause from 20% to 40% of pneumonias (Gilani et al. 2012; World Health Organization Pneumonia Vaccine Trial Investigators' Group 2001).

While the etiology of adult pneumonia has been more extensively studied, the same challenges are encountered as in studies of children. The estimated proportion of pneumonia cases caused by different pathogens varies between studies. This may represent a true difference in the underlying study populations or may be a result of different study design and methodology. A recent meta-analysis evaluated all published studies of pneumonia etiology in Europe from 1990-2011 (Rozenbaum et al. 2013). Seventy-seven studies were included, and inclusion criteria were strict, considering only radiologically confirmed pneumonia. The crude estimate of the proportion of pneumonia caused by *Streptococcus pneumoniae* was 19.3%. After adjusting for several variables using a fixed-effects meta-regression model, the estimated proportion of pneumococcal pneumonia in the average Northern European country was 15%. Another meta-analysis estimated pneumococcus to be the etiology of 24.8% of community acquired pneumonia (Said et al. 2013). In a prospective population-based study in Iceland, 373 consecutive patients admitted to Landspítali University Hospital for pneumonia were recruited and systematically tested for etiology (Bjarnason et al. 2015). Pneumococcus was found to be the causative agent in 28% of community acquired pneumonias, and 41% of health care-associated pneumonias. In a subsequent report of the same prospective cohort, the incidence of community acquired pneumonia was 21 per 10,000 person-years, and 20% were caused by pneumococci (Bjarnason et al. 2018).

### **1.1.2.2 *Health care burden of pneumonia***

Lower respiratory infections were, in 2016, estimated to cause 2,38 million deaths worldwide and were the sixth leading cause of death (Troeger et al. 2018). Of those deaths, 652,572 (95%CI 586,475 to 720,612) were estimated to occur among children under five years of age, making lower respiratory infections the leading cause of death in this age-group (Troeger et al. 2018). Large variations exist in the incidence, morbidity and mortality of pneumonia between countries (Troeger et al. 2018). Pneumonia disproportionately affects developing countries, which experience over half of the pneumonia associated mortality (Troeger et al. 2018). Yet pneumonia is still a large

health care burden in developed countries, and accounts for 3%-18% of all childhood hospital admissions (Madhi et al. 2012). In developed countries, the incidence of pneumonia in children under five years of age is 34-40 cases per 1,000 person-years (Madhi et al. 2012).

The burden of pneumonia is not isolated to mortality. Studies have shown a large impact on health-related quality of life that lasts for months after hospitalization for pneumonia (Andrade et al. 2018; Mangen et al. 2017), and in detailed cost analyses, hospitalized cases of pneumonia are associated with large direct and indirect monetary expenditure (Birnbaum et al. 2002; Keitel et al. 2014).

### **1.1.3 Invasive pneumococcal disease and mortality**

Invasive pneumococcal disease represents the most serious infectious presentation of *Streptococcus pneumoniae*. It occurs when pneumococcus gains access to normally sterile tissue. IPD is an umbrella term that compromises empyema, septic arthritis, bacteremia and meningitis.

The case-fatality ratio (CFR) of hospitalized pneumococcal bacteremia was reported to be 24.8% between 1952 and 1962 (Austrian 1964). Most patients died within five days of hospital admission despite antimicrobial treatment. Though the CFR has improved in the modern era, most patients who die, still do so within five days of hospitalization (Drijkoningen and Rohde 2014; Harboe et al. 2010; Mufson and Stanek 1999; Ladhami et al. 2013; Ricketson et al. 2013; Tsigrelis et al. 2008). The improvement in case-fatality is best demonstrated by a Swedish study which reported the incidence, case-fatality and mortality of hospitalized IPD from 1964 to 2008 (Backhaus et al. 2016). The overall CFR was 20% from 1964-1980, 15% from 1981-1995 and 9% from 1996-2008 (Backhaus et al. 2016). A report from an enhanced surveillance database of IPD in 26 European countries, documented CFR of 2.4% in children under five years of age, 9.1% in individuals 5-64 years of age, and 18.6% in adults 65 years of age and older (Torné et al. 2014). Pneumococcal serotypes have a variable propensity to cause death (Harboe et al. 2009; Hoek, Andrews, et al. 2012; Weinberger et al. 2010), and interactions between IPD CFR and seasonal influenza epidemics have been reported (Weinberger et al. 2013). However, a review of this is beyond the scope of this thesis.

Of the different manifestations of invasive disease, meningitis is associated with the highest CFR. The CFR of pediatric pneumococcal meningitis in Europe and the United States is estimated to be 38% and 8.4%

respectively (K. L. O'Brien et al. 2009; Hsu et al. 2009) From 1995-2005, the CFR of adult pneumococcal meningitis in Iceland was 8% (Þórðardóttir et al. 2014), and a CFR of 13% was documented for pediatric meningitis between 1975-2010 (Snaebjarnardóttir et al. 2013). Of those who survive, morbidity is common. In a single-center case series of pneumococcal meningitis, only 48% of patients were discharged from hospital with good neurological outcome (Kastenbauer and Pfister 2003). Another such study demonstrated long-term neurological sequelae in 30% of survivors (Weisfelt et al. 2006). The proportion of surviving children experiencing morbidity is even higher, with 49% having one or more long-term sequelae (Chandran et al. 2011). The effect of these conditions on health-related quality of life is devastating (Oostenbrink, A Moll, and Essink-Bot 2002).

## 1.2 Pneumococcal vaccines

In this chapter the history of pneumococcal vaccination is reviewed to better understand the current vaccine climate. Special attention is paid to the scientific discourse that led to conjugating pneumococcal polysaccharides to a protein carrier. The scientific literature on the impact of pneumococcal conjugate vaccines on acute otitis media, pneumonia and invasive pneumococcal disease is reviewed and discussed.

### 1.2.1 A brief history of pneumococcal vaccination

The history of pneumococcal vaccination can roughly be divided into three phases; the inactivated (killed) whole-cell vaccines; the polysaccharide vaccines and the conjugated vaccines. In George Sternberg's original description of pneumococcus in 1881, he observed that rabbits who were injected with saliva mixed with alcohol and quinine died less frequently than those injected with saliva alone, and were later resistant to re-injection with saliva (Austrian 1999; Sternberg 1882). Sternberg had inadvertently immunized the laboratory animals against subsequent infection by injecting killed pneumococci, thereby foreshadowing the concept of pneumococcal vaccination 30 years before it was first attempted in 1911 (Austrian 1999). In 1911, Wright and colleagues tested an inoculation of heat-killed pneumococcus to vaccinate South African miners against pneumococcal pneumonia (Wright et al. 1914). The trial failed to demonstrate efficacy because the significance of serotypes and serotype specific immunogenicity was not known at the time (Austrian 1999). In the following two decades, several trials using inactivated whole-cell pneumococcal vaccines were published (Cecil 1918; Lister 1916; Lister and Ordman 1936; Maynard 1913)

Due to inconsistencies in study design, the efficacy of whole bacteria pneumococcal vaccines remained fiercely debated at the time, despite some evidence of benefit (Austrian 1999).

Following discoveries of the immunogenicity of the polysaccharide capsule in the 1920s and 1930s (Dochez and Avery 1917; Finland 1931; Francis and Tillett 1930; Heidelberger and Avery 1923; Schiemann and Casper 1927), inactivated whole-cell pneumococcal vaccines were soon replaced with polysaccharide vaccines. The first clinical trial of a pneumococcal polysaccharide vaccine was conducted in the 1930s on 29,000 adult males in the American Civilian Conservation Corps using a bivalent vaccine (Ekwurzel et al. 1938). With similar methodological problems of previous trials of the inactivated vaccines, the results were debated. A second large trial was conducted in the late 1930s, using a tetravalent polysaccharide vaccine (Macleod et al. 1945). This trial built upon the experience of previous trials, and was able to show convincing efficacy against pneumococcal pneumonia, leading to the licensure of two hexavalent polysaccharide pneumococcal vaccines in the 1940s (Austrian 1999). One was formulated for adults and the other for children, each optimized to the serotype distribution within the respective age-group (Austrian 1999). Unfortunately, these early vaccines fell victim to unfavorable timing; in 1944, Tillett and colleagues showed that bacteremic pneumococcal pneumonia could be cured by parenteral administration of benzylpenicillin (Tillett, Cambier, and McCormack 1944). With this discovery, the medical community became complacent. The mortality rate of pneumococcal disease decreased sufficiently that there was no longer a perceived need for preventative vaccination. The licenses for the polysaccharide vaccines were withdrawn by the manufacturer due to lack of use (Austrian 1999). Interest in pneumococcal vaccination re-emerged in the 1950s when it was noted that the mortality benefit of penicillin was not ubiquitous. The elderly and those who had underlying disease did not experience a decrease in their case fatality ratio (Austrian 1964). This led to a redoubled effort to create a new polysaccharide vaccine. Several large randomized controlled trials were conducted in South Africa in the 1970s (Austrian et al. 1976; Smit 1977) and, based on these, a 14-valent pneumococcal vaccine was licensed in the United States in 1977. Its valency was increased to 23 polysaccharides in 1983 (Austrian 1999).

Early in the development of pneumococcal vaccines, there was an interest in vaccinating children. Two trials were conducted in the early 1980s which tested the use of polysaccharide vaccines on young children. Neither showed

benefit (Mäkelä et al. 1981; Sloyer, Ploussard, and Howie 1981). This result was not entirely unexpected. In 1937, The first polysaccharide trial conducted in children failed to detect any immunological response (Davies 1937). Laboratory studies in the 1930s and 1940s revealed that a response could be induced by adding a protein adjuvant (Austrian 1999). Several different pneumococcal conjugate vaccines entered phase II and phase III clinical trials in the late 1990s (Austrian 1999). The first of these to receive licensure was the seven valent pneumococcal conjugate vaccine, licensed in 2000 in the United States (Austrian 1999). It included the purified polysaccharides of seven serotypes of pneumococcus (4, 9V, 14, 19F, 23F, 18C and 6B) conjugated to CRM197 (PCV7<sub>CRM197</sub>), a nontoxic variant of the diphtheria toxin. It was shown to be efficacious for IPD, pneumococcal pneumonia and AOM in several randomized trials (Black et al. 2000; S. B. Black et al. 2002; Eskola et al. 2001; Fireman et al. 2003; O'Brien et al. 2003, 2008). In the 2000s, higher valency conjugated vaccines were developed and received licensure, based on the randomized trials conducted for the heptavalent conjugated vaccine. They have been shown to be effective in several cluster randomized trials and observational studies.

## **1.2.2 The impact of pneumococcal conjugate vaccines on otitis media**

Bacterial acute otitis media is still most often caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* despite changes in otopathogens (Ngo et al. 2016). It was used as an outcome measure in the earliest trials of pneumococcal polysaccharide vaccines (Mäkelä et al. 1981; Sloyer, Ploussard, and Howie 1981). In the following sub-chapters, evidence regarding the efficacy and impact of PCV on otitis media will be reviewed. Randomized controlled trials will be reviewed in greater depth, as they represent the highest quality of evidence of true efficacy. Observational studies will be reviewed more generally.

### **1.2.2.1 Randomized controlled trials evaluating the efficacy of pneumococcal conjugate vaccines for otitis media**

Eight randomized controlled trials have examined the efficacy of pneumococcal conjugate vaccines on acute otitis media (Black et al. 2000; Dagan et al. 2001; Eskola et al. 2001; Fireman et al. 2003; Kilpi et al. 2003; O'Brien et al. 2008; A. Palmu et al. 2015; Prymula et al. 2006; Tregnaghi et al. 2014; Vesikari et al. 2016). Six trials reported the efficacy for vaccine-type pneumococcal AOM and pneumococcal AOM regardless of serotype revealing large and statistically significant effects. Six trials demonstrated a

moderate efficacy against all-cause AOM, but only three reached statistical significance. The studies are summarized in Table 3.

The first published randomized controlled trial of a pneumococcal conjugate vaccine reported, among other outcomes, the efficacy against AOM (Black et al. 2000). The study recruited 37,868 children and randomized them to the either PCV7<sub>CRM197</sub> or the meningococcus C CRM197 conjugate vaccine. A separate publication from the same trial examined the effect of PCV7<sub>CRM197</sub> on AOM in more detail using the full data (Fireman et al. 2003). The estimated vaccine efficacy against otitis media visits was 7.8% (95%CI 5.4% to 10.2%). Slightly higher point estimates were found for otitis media episodes, frequent otitis media and ventilatory tube placements (Black et al. 2000; Fireman et al. 2003)

The following year the results of two more randomized controlled trials were published (Dagan et al. 2001; Eskola et al. 2001). Dagan et al. (2001) enrolled 264 children ages 12-35 months of age attending eight daycare centers in Beer-Sheva, Isreal. The study's primary endpoint was vaccine-type nasopharyngeal carriage and the secondary endpoint was parent-reported respiratory infections. The study reported an efficacy of 17% (95%CI -2% to 33%) for otitis media episodes and 20% (95%CI 14% to 26%) for antimicrobial treated otitis media, as measured by days spent on antimicrobials.

The later study published in 2001 compared two heptavalent pneumococcal conjugate vaccine to a hepatitis B vaccine control (Eskola et al. 2001; Kilpi et al. 2003). The two heptavalent pneumococcal vaccines differed in their use of carrier protein. One was the same vaccine as in the Black et al. (2000) study (PCV7<sub>CRM197</sub>), and the other was conjugated to meningococcal outer membrane protein complex (PCV7<sub>MOMP</sub>C). The Eskola et al. (2001) paper reported comparison of the PCV7<sub>CRM197</sub> to the hepatitis B vaccine. The analogous comparison of the PCV7<sub>MOMP</sub>C was reported in a separate publication (Kilpi et al. 2003). No head-to-head comparison of the two heptavalent vaccines was ever reported.

A total of 2,497 children were enrolled, of which 835 received the PCV7<sub>MOMP</sub>C vaccine and were therefore not reported in the Eskola et al. (2001) paper. If AOM was diagnosed as defined by the study criteria, myringotomy and aspiration of middle-ear fluid were performed and samples sent for culture. The results were most consistent with a 6% efficacy against all-cause AOM with 95% confidence limits of -4% and 16%. The study was also one of the first to demonstrate clinically relevant serotype replacement,

showing a 33% (95%CI -1%-80%) increase in pneumococcal AOM caused by serotypes not included in the vaccine.

The effect estimates for the PCV<sub>7MOMP</sub> against culture-confirmed pneumococcal AOM was 25% (95%CI 11%-37%) and was 56% (95%CI 44%-66%) for the seven serotypes included in the vaccine (Kilpi et al. 2003). However, unlike PCV<sub>CRM197</sub>, it did not seem to confer protection against cross-reactive serotypes. Interestingly, virtually no effect was seen on all-cause AOM with this vaccine preparation. The effect estimate was -1% (95%CI -12% to 10%).

Table 3. Randomized controlled trials evaluating the efficacy of pneumococcal conjugate vaccines for acute otitis media (AOM) and tympanostomy procedures. Vaccine efficacy is presented along with 95% confidence intervals for vaccine-type AOM, pneumococcal AOM, all-cause AOM, recurrent AOM (rAOM) and tympanostomy tube placements (TTP). Information that was not reported in a particular trial is indicated with a hyphen (-). Some studies did not present intention to treat estimates. In those cases, per-protocol efficacy estimates are presented and indicated with an asterisk (\*)

Study	Vaccine-type AOM	Pneumococcal AOM	All-cause AOM	rAOM	TTP
Black et al. (2000); Fireman et al. (2003)	65% (not specified)	-	7.8% (5.4% to 10.2%)	9% (3% to 15%)	20% (2% to 35%)
Dagan et al. (2001)	-	-	17% (-2% to 33%)	-	-
Eskola et al. (2001)	54% (41% to 64%)	34% (21% to 45%)	6% (-4% to 16%)	16% (-6% to 35%)	4% (-19% to 23%)
Kilpi et al. (2003)	56% (44% to 66%)*	25% (11% to 37%)	-1% (-12% to 10%)	-	-
Prymula et al. (2006)	53% (35% to 66%)	52% (37% to 63%)	33.6% (20.8% to 44.3%)*	56% (-2% to 81%)	60% (-27% to %88)

O'Brien et al. (2008)	64% (-34% to 90%)*	-	-0.4% (-19.4% to 15.6%)	5% to 41%)	28% (-52% to 84%)
Tregnaghi et al. (2014)	69.9% (29.8% to 87.1%)	55.7% (21.5% to 75%)	19% (4.4% to 31.4%)	-	-
A. Palmu et al. (2015); Vesikari et al. (2016)	-	-	6.4% (-5.5% to 17.2%)	-	13% (-2% to 26%)

In 2006, Prymula et al. (2006) reported a randomized study of an 11-valent pneumococcal conjugate vaccine in 4,968 children recruited from pediatric centers in the Czech Republic and Slovakia (Prymula et al. 2006). The 11-valent vaccine was conjugated to *Haemophilus influenzae* protein D, and one of the study aims was to estimate the efficacy against AOM caused by non-typeable *Haemophilus influenzae*. In the intention to treat analysis, the vaccine efficacy for the first occurrence of AOM caused by pneumococcus was 52.6% (95%CI 36.1% to 65.5%) and was 32.7% (95%CI 0.77% to 54.3%) for the first occurrence of AOM caused by NTHi. Only per-protocol efficacy was presented for all-cause AOM, which was estimated to be 33.6% (20.8% to 44.3%).

In 2003, the first paper from a cluster randomized controlled trial of PCV7<sub>CRM197</sub> among the Navajo and White Mountain Apache infants was published (O'Brien et al. 2003), and in 2008, a retrospective chart review of AOM visits among the participating children was published (O'Brien et al. 2008). The study population was defined as children who had adhered to the study protocol, i.e. a per-protocol analysis. From this population, 944 of the 4,476 eligible children were randomly sampled for chart review. No difference was found between the PCV7<sub>CRM197</sub> arm and the control, with an estimated vaccine efficacy of -0.4% (95%CI -19.4%-15.6%).

Tregnaghi et al. (2014) reported a randomized controlled trial of PHID-CV10 conducted in Argentina, Panama and Colombia with an enrollment period from 2007-2011. The primary outcome was bacterial community acquired pneumonia in the per-protocol cohort, and the first secondary outcome was clinically diagnosed AOM. All clinically suspected cases of AOM were subsequently referred to otolaryngologists associated with the

study, who confirmed the diagnosis and performed tympanocentesis if middle ear fluid was present. The study reported a 19% (95%CI 4.4% to 31.4%) vaccine efficacy for clinically diagnosed AOM in the intention to treat analysis. The estimated efficacy for pneumococcal AOM was 55.7% (95%CI 21.5% to 75%) and the estimated efficacy for vaccine-type AOM was 69.9% (95%CI 29.8% to 87.1%). Unlike Prymula et al. (2006), the study did not find a statistically significant efficacy against AOM caused by NTHi, though the point estimate was similar 21.5% (95%CI -43.4% to 57.0%) (Tregnaghi et al. 2014).

Finally, the results of a cluster-randomized controlled trial on AOM and tympanostomy tube placements conducted in Finland in 2009 were reported in two publications (A. Palmu et al. 2015; Vesikari et al. 2016). The details of the trial are outlined in Chapter 1.2.4. Tympanic tube placements were evaluated in the main trial, while the efficacy against AOM was evaluated in a smaller trial, nested within the main trial. Vaccine efficacy for tympanic tube placements was 13% (95%CI -2% to 26%) (A. Palmu et al. 2015). The efficacy of parent-reported, physician diagnosed AOM was assessed with active surveillance through means of text messaging, and was estimated as 6.4% (95%CI -5.5% to 17.2%) (Vesikari et al. 2016).

Taken together, six randomized controlled trials of pneumococcal conjugate vaccines demonstrated a large and consistent decrease in pneumococcal AOM, with estimates ranging from 53% to 70% for vaccine-type disease and 25% to 56% for pneumococcal disease regardless of serotype (Black et al. 2000; Eskola et al. 2001; Fireman et al. 2003; Kilpi et al. 2003; O'Brien et al. 2008; Prymula et al. 2006; Tregnaghi et al. 2014). The effects on all-cause AOM were less consistent. All eight randomized trials reported the effect on all-cause AOM, with estimates ranging from -1% to 34% (Black et al. 2000; Dagan et al. 2001; Eskola et al. 2001; Fireman et al. 2003; Kilpi et al. 2003; O'Brien et al. 2008; A. Palmu et al. 2015; Prymula et al. 2006; Tregnaghi et al. 2014; Vesikari et al. 2016). Five trials tested a seven-valent pneumococcal conjugate vaccine, with effect estimates ranging from -1% to 17% (Black et al. 2000; Dagan et al. 2001; Eskola et al. 2001; Fireman et al. 2003; Kilpi et al. 2003; O'Brien et al. 2008). Of those, only Fireman et al. (2003) reached statistical significance. Three trials tested PHiD-CV10 or its 11-valent predecessor (A. Palmu et al. 2015; Prymula et al. 2006; Tregnaghi et al. 2014; Vesikari et al. 2016). The effect estimates were larger, ranging from 6% to 34%, and two of the three studies reached statistical significance (Prymula et al. 2006; Tregnaghi et al. 2014). The results of the randomized controlled trials provide a plausible range within

which the vaccine impact as estimated by observational studies are likely to fall.

### ***1.2.2.2 Observational studies evaluating the impact of pneumococcal conjugate vaccines for otitis media.***

The observational studies discussed in this chapter were obtained from two systematic reviews of the impact of pneumococcal conjugate vaccines on otitis media (Taylor et al. 2012; Vojtek, Nordgren, and Hoet 2017). Nine studies were included and reported impact ranging from -7% to 29%, with large variations in case definition and methodology (Ben-Shimol et al. 2014; Grijalva et al. 2006; Grijalva, Nuorti, and Griffin 2009; Poehling 2004; Poehling et al. 2007; Lau et al. 2015; Magnus et al. 2012; Marom et al. 2014; Singleton et al. 2009). The discussion will focus on if and how the studies accounted for secular trends in the incidence of AOM prior to the introduction of PCV, and whether population-based data were used.

Eight of the nine studies included acknowledged an observed decreasing trend of AOM prior to vaccine introduction (Grijalva et al. 2006; Grijalva, Nuorti, and Griffin 2009; Poehling 2004; Poehling et al. 2007; Lau et al. 2015; Magnus et al. 2012; Marom et al. 2014; Singleton et al. 2009). However, only three attempted to correct for the observed secular trend. Grijalva et al. (2006) employed a crude difference-in-differences approach, in which the relative risk ratio between young vaccine eligible children and older vaccine non-eligible children in the pre- and post-vaccine periods were compared. This approach assumes that secular trends in AOM are identical in children under the age of three, and between three and six years of age and that no other changes than vaccination occurred that could upset this balance. This resulted in an estimated impact of 0.80 (95%CI 0.66 to 0.96).

Lau et al. (2015) and Marom et al. (2014) used a variation of linear interrupted time series analysis. Interrupted time series analysis is a segmented regression, which fits a linear trend in a defined pre-intervention period, and compares this to a linear trend in a defined post-intervention period (Penfold and Zhang 2013; Wagner et al. 2002). The major threats to the validity of such analyses are few pre- and post-intervention observations, the existence of other possible changes that correlate with the intervention and inappropriate use of linear trends (Jandoc et al. 2015). Lau et al. (2015) demonstrated a roughly 20% sequential decrease in the incidence of otitis media among children younger than 10 years of age following the introduction of PCV7 and PCV13. There do not seem to be obvious threats to the validity of this study. In Marom et al. (2014), a version of segmented

linear regression was performed on 11 annual incidence estimates of otitis media to estimate the added benefit of PCV13 over PCV7. A linear trend was constructed from eight of these estimates, which was then projected without any uncertainty over the last two years of the study period. Any difference between the observed incidence of otitis media and the projected line is assumed to be due to the effect of PCV13. Projected trends are subject to uncertainty and should not be used as a baseline truth. Furthermore, the number of observations used in the regression was extremely few, rendering segmented regression inappropriate (Jandoc et al. 2015).

Ben-Shimol et al. (2014) did not specifically discuss whether a trend was occurring in the pre-vaccine period. They report a detailed prospective population-based study of pathogen specific otitis media, which included a four year period prior to vaccine introduction. Visual inspection of the included figures seems to reveal an abrupt decrease in pneumococcal AOM one year prior to the introduction of PCV7. This is said to be due to the private market availability of the vaccine one year before general introduction into the pediatric vaccination program. However, only 18% of children younger than one year of age had received two or more vaccine doses when the decrease was visually underway. It is also not clear from the publication whether the rate of tympanocentesis among children presenting with AOM decreased disproportionately following vaccine introduction. This could independently explain the observed decrease in pneumococcal AOM, but would not confound the substantial decrease in vaccine-type pneumococcal AOM. Of the included studies, only Ben-Shimol et al. (2014) used population-based data.

Observational studies that have examined the impact of pneumococcal conjugate vaccines on otitis media have generally reported significant decreases. The magnitude and direction of the impact estimates were consistent with the results of the randomized controlled trials. Six of the nine studies providing observational evidence of impact were conducted in the United States (Grijalva et al. 2006; Grijalva, Nuorti, and Griffin 2009; Poehling 2004; Poehling et al. 2007; Marom et al. 2014; Singleton et al. 2009). Of the nine studies, only three made some attempt to adjust for the secular trends (Grijalva et al. 2006; Lau et al. 2015; Marom et al. 2014). The only population-based study examining PCV impact reported the impact on otitis media requiring tympanocentesis, a selective outcome measure that represents the minority of otitis media cases (Ben-Shimol et al. 2014). No population-based observational study has been reported that examines the

impact of PCV on outpatient physician-diagnosed otitis media in primary care.

### **1.2.3 The impact of pneumococcal conjugate vaccines on pneumonia**

Four randomized controlled trials have evaluated the efficacy of pneumococcal conjugate vaccines for pneumonia (S. B. Black et al. 2002; Cutts et al. 2005; Kilpi et al. 2018; Tregnaghi et al. 2014). In 2005, the World Health Organization published a consensus statement defining WHO criteria for pneumonia (Cherian et al. 2004). S. B. Black et al. (2002), Tregnaghi et al. (2014) and Kilpi et al. (2018) are reports from randomized controlled trials that are extensively reviewed in Chapters 1.2.2.1 and 1.2.4. S. B. Black et al. (2002) reported the intention to treat efficacy estimate of the secondary endpoint of clinically diagnosed pneumonia to be 6% (95%CI -1.5% to 11%). Following the development of the WHO-criteria (Cherian et al. 2004), the data was re-analyzed and the efficacy against WHO-criteria radiographically confirmed pneumonia was 25.5% (95%CI 6.5% to 40.7%) (Hansen et al. 2006). Tregnaghi et al. (2014) reported the intention to treat analysis efficacy estimate of the primary outcome of bacterial community acquired pneumonia as 18.2% (95% 5.5% to 29.1%), and secondary end-points included clinically suspected pneumonia, 7.3% (95%CI 2.1% to 12.3%). Finally, Kilpi et al. (2018) reported efficacy estimates for hospital-diagnosed pneumonia to be 27% (95%CI 14% to 38%) and radiographically confirmed pneumonia as 28% (95%CI 5% to 46%).

Cutts et al. (2005) reported the results of a randomized controlled trial of 17,437 children recruited in the Gambia from 2000 to 2003, who received either a nine-valent pneumococcal vaccine conjugated to CRM197, or the diphtheria-pertussis-tetanus vaccine. At the time of publication, the WHO consensus statement on radiographically confirmed pneumonia had not yet been published. However, the study did employ WHO trained radiologists. The efficacy for clinically and radiographically diagnosed pneumonia was 7% (95%CI 1% to 12%) and 37% (95%CI 25% to 48%) respectively. The results of the randomized controlled trials are summarized in Table 4.

Table 4. Randomized controlled trials evaluating the efficacy of pneumococcal conjugate vaccines for pneumonia. Vaccine efficacy is presented along with 95% confidence intervals. Radiographically confirmed pneumonia is based on WHO-criteria (Cherian et al. 2004). Cutts et al. (2005) did not report intention to treat estimates and did not report WHO-criteria radiographically confirmed pneumonia. The per-protocol radiographically confirmed pneumonia estimates using the study's criteria are presented. These are indicated with an asterix (\*). Kilpi et al. (2018) only reported hospital-diagnosed pneumonia, not clinically suspected pneumonia (\*\*)

Study	No. of children	Clinically suspected pneumonia	Radiographically confirmed pneumonia
S. B. Black et al. (2002); Hansen et al. (2006)	37,868	6 (-1.5 to 11)	25.5% (6.5% to 40.7%)
Cutts et al. (2005)	17,437	7% (1% to 12%)*	37% (25% to 48%)*
Tregnaghi et al. (2014)	23,821	7.3% (2.1% to 12.3%)	18.2% (5.5% to 29.1%)
Kilpi et al. (2018)	6,178	27% (14% to 38%)**	45% (26% to 60%)

A multitude of observational studies evaluating the effect of the introduction of pneumococcal conjugate vaccines on pneumonia have been published. They use different case definitions and design, and reviewing each study individually is beyond the scope of this thesis. A systematic review of pneumonia impact studies identified 60 publications, with 60% of studies finding significant reductions in clinically diagnosed pneumonia and 55% showing reductions in radiographically confirmed pneumonia (Jennifer D. Loo et al. 2014). Most of the included studies did not use controls or correct for pre-vaccine time-trends, however no attempt was made to summarize the studies with regards to methodological factors. The impact estimates for clinical pneumonia ranged from 13% to 39% (Ansaldi et al. 2008; De Wals et al. 2008; Grijalva et al. 2007; Koshy et al. 2010; Jennifer D. Loo et al. 2014; Simonsen et al. 2011). In another systematic review and meta-analysis of the impact of PCV10 and PCV13 on pneumonia, the quality of the studies was analyzed and a random-effect model was used to summarize the results (Alicino et al. 2017). This review included 12 studies, of which only six adjusted for secular trends and five used some form of control – most often total hospital admissions. The meta-analysis concluded that in children aged 24 months and younger, the introduction of the higher valency conjugate vaccines resulted in a 17% (95%CI 11% to 22%) reduction in clinical pneumonia and a 31% (95%CI 26% to 35%) in radiographically confirmed pneumonia (Alicino et al. 2017).

In conclusion, randomized controlled trials have shown that the efficacy of PCV for clinically suspected pneumonia was 7% (Cutts et al. 2005; Hansen et al. 2006; Tregnaghi et al. 2014). However, in the population of children

who presented to a hospital, the effectiveness of PCV for clinically suspected pneumonia was 27% (Kilpi et al. 2018). Efficacy estimates for radiographically confirmed pneumonia ranged from 18% to 37% (Cutts et al. 2005; Hansen et al. 2006; Kilpi et al. 2018; Tregnaghi et al. 2014). A large number of observational studies examining PCV impact on pneumonia have been published indicating an impact on clinically diagnosed pneumonia ranging from 13% to 39% (Ansaldi et al. 2008; De Wals et al. 2008; Grijalva et al. 2007; Koshy et al. 2010; Jennifer D. Loo et al. 2014; Simonsen et al. 2011). A meta-analysis of impact studies estimated the impact to be 17% (Alicino et al. 2017).

#### **1.2.4 The impact of pneumococcal conjugate vaccines on invasive pneumococcal disease**

Invasive pneumococcal disease represents an optimal outcome for trialists to evaluate with randomized controlled trials. It is diagnosed when *Streptococcus pneumoniae* is cultured from normally sterile bodily fluids – there is little risk of subjectivity bias in the outcome. Five randomized controlled trials evaluated the efficacy of PCV for IPD, of which four have been extensively reviewed in Chapters 1.2.2.1 and 1.2.3 (Black et al. 2000; Cutts et al. 2005; O'Brien et al. 2003; Palmu et al. 2013; Tregnaghi et al. 2014). Black et al. (2000) reported the efficacy of PCV7 for vaccine-type IPD to be 93.9% (95%CI 79.6% to 98.5%). One fully vaccinated child was diagnosed with IPD caused by 19F. The vaccine-efficacy against IPD regardless of serotype was 89.1% (73.7% to 95.85%). Cutts et al. (2005) only reported the per-protocol estimates of vaccine efficacy, which were 77% (95%CI 51% to 90%) and 50% (95%CI 21% to 69%) for vaccine-type and all-cause IPD respectively. The only randomized controlled trial to report statistically non-significant results of PCV on all-cause IPD was O'Brien et al. (2003), with 46.3% (95%CI -16.5% to 75.3%) in the intention to treat analysis. The efficacy against vaccine-type IPD was 86.4% (95%CI 40.3% to 96.9%). Tregnaghi et al. (2014) did not include IPD as the primary or first secondary outcome measure. They reported a 100% (95%CI 77.3% to 100%) efficacy for vaccine-type IPD and a 66.7% (95%CI 21.8% to 85.9%) efficacy for all-cause IPD.

Palmu et al. (2013) reported a cluster-randomized controlled trial in Finland, in which 47,366 children were randomized to either PHiD-CV10 or Hepatitis A vaccine from February 2009. The primary outcome was vaccine-type IPD among children who received at least one dose of PHiD-CV10 before seven months of age, in the three primary dose + one booster dose

schedule. The efficacy for vaccine-type IPD among children who were randomized to the 3+1 schedule and received at least one dose before seven months of age, was 100% (95%CI 83% to 100%). The efficacy for children randomized to the 2+1 schedule was 92% (95%CI 58% to 100%). The intention to treat estimate of the vaccine efficacy for the combined 2+1 and 3+1 group was not reported – the per-protocol estimate was 100% (95%CI 91% to 100%) Finally, the efficacy for IPD regardless of serotype in the combined 2+1 and 3+1 schedules was 93% (95%CI 75% to 99%). The results of the randomized controlled trials are summarized in Table 5.

Table 5. Randomized controlled trials evaluating the efficacy of pneumococcal conjugate vaccines for invasive pneumococcal disease (IPD). Vaccine efficacy for vaccine-type IPD, and IPD regardless of serotype are presented along with 95% confidence intervals. Some studies did not present intention to treat estimates. In those cases, per-protocol efficacy estimates are presented and indicated with an asterix (\*)

Study	No. of children	Vaccine-type IPD	IPD regardless of serotype
Black et al. (2000)	37,868	93.9% (79.6% to 98.5%)	89.1% (73.7% to 95.85%)
Cutts et al. (2005)	17,437	77% (51% to 90%)*	50% (21% to 69%)*
O'Brien et al. (2003)	856	86.4% (40.3% to 96.9%)	46.3% (-16.5% to 75.3%)
Tregnaghi et al. (2014)	23,821	100% (77.3% to 100%)	66.7% (21.8% to 85.9%)
Palmu et al. (2013)	47,366	100% (91% to 100%)*	93% (77% to 99%)

Too many observational studies of the impact of pneumococcal conjugate vaccines on invasive pneumococcal disease have been published for them to be individually reviewed in this thesis (Myint et al. 2013). A systematic review and meta-analysis of all published studies in high-income countries from 1994-2010 identified 242 publications and summarized the results with a Bayesian random-effect model (Shiri et al. 2017). The model was used to predict the time in years from the introduction of a PCV into a country's pediatric vaccination program, until a 50% and 90% reduction in vaccine-type IPD had occurred in the whole country's population. The average time until a 50% reduction in vaccine-type IPD was observed was 2.3 years (95%

credible intervals 1.9 to 2.7), and the average time to 90% reduction was 8.9 years (95% credible intervals 7.8 to 10.3) (Shiri et al. 2017).

### **1.3 Cost-effectiveness in the context of pneumococcal conjugate vaccination**

Health care operates under resource constraints. In this setting of scarcity, the decision to fund one project inevitably results in another project remaining unfunded (Danzon et al. 2018). Economic analyses are one of many tools to aid decision-makers in allocating resources optimally. Interventions are compared with two or more alternatives, and costs and benefits are systematically scrutinized (Szucs 2005). Economic analyses require data on the efficacy of the interventions being evaluated, the burden of disease, and the subgroups of the population which are affected (Gray et al. 2011).

All methods of economic analysis measure the monetary costs associated with the relevant interventions, but differ in how they measure the resultant benefits (Gray et al. 2011). Cost-benefit analysis translates the effect of an intervention into a monetary value, and calculates the total cost associated with the intervention once any potential savings have been applied (Svensson and Hultkrantz 2017). In cost-effectiveness analysis, the effect of the intervention is measured in units of the condition being intervened upon, e.g. number of deaths prevented, years of life gained (Svensson and Hultkrantz 2017). The results of such an analysis are commonly presented as an incremental cost-effectiveness ratio, which represents the cost associated with one unit change in the effect measure (Gray et al. 2011). Cost-effectiveness analyses are preferred over cost-benefit analyses in the health care context, as first converting health-benefit to a single monetary value is impractical and is in most cases tangential to the research question (Culyer and Chalkidou 2019). One drawback however, is the difficulty of comparing cost-effectiveness ratios between studies that use different measurements of effect. Cost-utility analyses remedy this by standardizing a combined effect that measures both the quality and quantity of life gained (Gray et al. 2011). This combined effect is most often measured in units of quality-adjusted life-years (QALY) (Gray et al. 2011).

Quality-adjusted life-years are determined by dividing each person's life into units of time (Prieto and Sacristán 2003). A unit of time lived in perfect health is assigned a value of one, while death is assigned a value of zero. Each disease is assigned a utility, which represents the health-related quality of life an individual is expected to have while suffering from the disease (Gray et al. 2011). Three methods are generally used to obtain utility values for a

given health state. These are termed the rating scale method, the time trade-off and the standard gamble (Prieto and Sacristán 2003). Each method is intended to capture the preferences of the population to which the economic analysis pertains, and they are not meant to be generalized to other populations except with extreme caution (Petrou and Kupek 2009).

Measuring costs associated with an intervention is deceptively simple. They depend on from which perspective the intervention is evaluated (Byford and Raftery 1998). When examined from the societal perspective, an expensive medication may be cost-saving if it allows individuals who would have otherwise required disability benefits to participate in the workforce. The same medication may be considered prohibitively costly when examined from the health care perspective (Byford and Raftery 1998). The choice of perspectives should reflect the purpose of the analysis and the intended audience. In health-economic analysis of vaccines, the general consensus is to choose the societal perspective, but also include an analysis from the perspective of the health care sector (Sanders et al. 2016).

Interventions are compared at a single point in time but accrue costs and benefits over a variably long time period. Time horizon is the term used for the period of time over which an intervention is evaluated (Gray et al. 2011). In general, the time horizon should be chosen to reflect the duration of the intervention's effect. In the context of cost-effectiveness analyses of vaccines, the consensus is to use a lifetime horizon, unless there are compelling reasons otherwise (Mauskopf et al. 2018; Wilkinson et al. 2016). To accurately compare interventions with differential distributions in the timing of costs and benefits, it has become standard practice to discount future cost and benefit (Attema, Brouwer, and Claxton 2018). The rationale is grounded in both the psychology of human behavior and in economic principles (Severens and Milne 2004). Society tends to value current costs and benefits higher than those that occur in the future. The exact discount rate, whether it should be a constant rate, and whether costs and benefits should be discounted at the same rate, are all debated (Claxton et al. 2011). However, the general consensus is to use a constant 3% discount rate for both costs and benefits (Mauskopf et al. 2018; Sanders et al. 2016; Wilkinson et al. 2016).

Economic analyses are built upon a set of assumptions that may influence the outcome. In the case of pneumococcal conjugate vaccines, the assumptions include the incidence of disease in the target population, the proportion caused by *Streptococcus pneumoniae*, the serotype distribution,

the degree of vaccine uptake, the vaccine efficacy in vaccinated and unvaccinated members of the population, costs and utilities associated with disease states, cost of the vaccine, perspective, time horizon and discounting (Wasserman et al. 2018). These assumptions are combined together in a mathematical model which generates an outcome, given the input parameters (Weinstein et al. 2001). Decision analysis models are static scenario-based models in which individuals are assumed to progress independently through a decision tree (Weinstein et al. 2003). The tree has one branch for each intervention being evaluated, and each branch contains an identical set of nodes that represent the health outcomes being considered. However, the nodes on each branch are defined by a different set of costs, consequences and probabilities of occurring. The model is run and the number of individuals in each node are tallied, along with the associated costs and consequences, producing a final result. Generally, this model requires the assumption that probabilities are fixed, and do not vary depending on age or elapsed time (Gray et al. 2011). For example, a decision analysis model would assume that the difference in the probability of contracting pneumonia with and without the vaccine was constant, regardless of the years elapsed since vaccine introduction (Kim and Goldie 2008; Weinstein et al. 2003).

Markov models expand upon this framework by removing the tree structure and allowing individuals to transition in any direction between nodes, which are termed “health states” in Markov models (Gray et al. 2011; Siebert et al. 2012). In these models, the transitions between health states occur in cycles. At the end of each cycle, the costs and consequences associated with the current health state are recorded, before the next cycle begins. Thus, an individual accumulates costs and benefits over time and may transition in and out of health states – an improvement over the static decision analysis models. The transition probabilities may either be constant or time-dependent. However, the Markovian assumption dictates that all individuals within a given health state are homogeneous, regardless of their previous health states or the length of time that they have been in their current state (Siebert et al. 2012). Thus, the transition between health states may depend on the time that has elapsed from the start of the model, but cannot depend on what has happened in a prior cycle (Gray et al. 2011). A Markov model would assume that an individual who has previously been hospitalized twice for pneumonia, has the same probability of being hospitalized again as someone who has never been hospitalized. Transmission dynamic models expand upon the Markov process by using a

set of differential equations to annul the Markovian assumption (Pitman et al. 2012).

Because of the subjective nature of many of the modeling assumptions, a sensitivity analysis is necessary to explore the cost-effectiveness outcomes over a range of plausible input parameters. Consensus statements from the World Health Organization and the International Society for Pharmacoeconomics and Outcome Research (ISPOR) require, at minimum, a one-way sensitivity analysis of each of the assumptions (Mauskopf et al. 2018; Walker, Hutubessy, and Beutels 2010). One-way sensitivity analysis implies that each parameter is individually varied across its probability distribution, while other parameters are held at a constant value (Gray et al. 2011). The results are often presented as a tornado plot. Scenario analyses show the result of specific combinations of parameter values, which are often based on common situations that decision-makers may find useful (Gray et al. 2011). Both consensus statements strongly recommend the inclusion of a probabilistic sensitivity analysis (PSA), in which the analysis is repeatedly run and all parameters are simultaneously varied across their respective probability distributions (Gray et al. 2011). The resulting spread of cost-effectiveness estimates reflects the uncertainty of the analysis. This can be paired with threshold analysis, which shows the proportion of the resulting spread above a stated cost-effectiveness threshold, or a generalization of a threshold analysis called the cost-effectiveness acceptability curve (CEAC) (Gray et al. 2011).

A large number of cost-effectiveness analyses of pneumococcal conjugate vaccines have been published (Saokaew et al. 2016; Vooren et al. 2014; Wu et al. 2015). They display great variation in their results, underlying assumptions and modeling choices. In this thesis, cost-effectiveness analyses of pneumococcal conjugate vaccines in high-income countries will be reviewed. The studies included in this review are summarized in Table 6. This review focuses on studies published in 2009 and later, after the introduction of the higher-valent pneumococcal conjugate vaccines. Other published reviews have examined cost-effectiveness studies prior to 2006 (Beutels, Thiry, and Van Damme 2007), and studies in low- and middle income countries (Saokaew et al. 2016). All of the included studies found pneumococcal conjugate vaccines to be cost-effective compared to no vaccine, but varied as to whether PCV7, PCV10 or PCV13 was the dominant strategy (Saokaew et al. 2016; Vooren et al. 2014; Wu et al. 2015). The aim of this review is to explore the studies' design and underlying assumptions, rather than the results.

Table 6. A summary of the economic analyses of pneumococcal conjugate vaccines in high-income countries from 2009-2018. All analyses are either a cost-effectiveness analysis (CEA) or cost-utility analysis (CUA). Costs and benefits are considered either from the societal or health care perspective, depending on whether indirect costs such as productivity loss are included in the analyses. The time horizon of the studies is presented in years. A lifetime horizon is based on the life-expectancy of the population, and is most commonly assumed to be 100 years. Discount rates are presented separately for costs and benefits. When the time horizon is one year or less, discount rates are not applicable, and are presented with a hyphen (-). Earnshaw et al. (2012) did not publish sufficient information to determine what discount rate was used. The table is partially adapted from Wu et al. (2015).

Study	Study type	Perspective	Time horizon (years)	Discount rate of costs (%)	Discount rate of benefits (%)
M. A. O'Brien et al. (2009)	CUA	Societal	Lifetime	3	3
Chuck et al. (2010)	CUA	Health care	1	-	-
Rozenbaum et al. (2010)	CEA, CUA	Health care, societal	5	4	1.5
Rubin et al. (2010)	CUA	Societal	10	3	3
Talbird et al. (2010)	CEA, CUA	Societal	1	-	-
Robberstad et al. (2011)	CEA, CUA	Societal	Lifetime	4	4
Newall et al. (2011)	CUA	Health care	100	5	5
Díez-Domingo et al. (2011)	CEA, CUA	Health care	Lifetime	3	3
Knerer, Ismaila, and Pearce (2012)	CEA, CUA	Health care, societal	Lifetime	3, 3.5	3, 3.5
Earnshaw et al. (2012)	CUA	Health care	Lifetime	Not specified	Not specified
By et al. (2012)	CUA	Societal	Lifetime	3	3

Strutton et al. (2012)	CEA, CUA	Health care	1	-	-
Blank and Szucs (2012)	CEA, CUA	Health care	10	3	3
Hoek, Choi, et al. (2012)	CUA	Health care	30	3.5	3.5
Klok et al. (2013)	CEA, CUA	Health care	1	3	3
Zhou et al. (2014)	CUA	Health care, societal	Lifetime	3	3
Delgleize et al. (2016)	CUA	Health care, societal	Lifetime	3.5	3.5
Newall et al. (2016)	CUA	Health care	-	5	5
Castiglia et al. (2017)	CUA	Health care	18	3	3
Gouveia et al. (2017)	CEA	Societal	Lifetime	5	5
Kuhlmann and Schulenburg (2017)	CUA	Health care, societal	50	3	3

### 1.3.1 Vaccine efficacy assumptions in economic analyses of pneumococcal conjugate vaccines

Because *Streptococcus pneumoniae* causes a wide range of clinical infections, economic analyses of the cost-effectiveness of pneumococcal conjugate vaccines must choose which health outcomes to include in the analysis. Most, but not all, include acute otitis media, pneumonia and invasive pneumococcal disease. The studies include variable definitions of what constitutes each health outcome, assume differing baseline probabilities of the outcome occurring, and assume divergent vaccine efficacies for the included outcomes. Each of the health outcomes considered may or may not be associated with further health care consumption and disease burden. Repeated AOM may lead to a tympanostomy tube procedure, and IPD may cause death or long term disability. If and how disease sequelae are taken into account is variable between studies. Finally, the studies differ in whether

they consider health outcomes in unvaccinated members of the population (Holubar et al. 2017; Isaacman et al. 2008).

Most of the reviewed cost-effectiveness analyses based their vaccine efficacy estimates for AOM on the results of the Northern California Kaiser Permento trial (Black et al. 2000; Fireman et al. 2003). A large proportion of the remaining studies (Castiglia et al. 2017; Delgleize et al. 2016; Klok et al. 2013; Knerer, Ismaila, and Pearce 2012; Robberstad et al. 2011; Strutton et al. 2012; Talbird et al. 2010) based their efficacy of PCV7 and PCV13 on Eskola et al. (2001). These studies often justified a higher vaccine efficacy estimate for PHiD-CV10 based on Prymula et al. (2006) or Tregnaghi et al. (2014), by also assuming efficacy for AOM caused by non-typeable *Haemophilus influenzae*. The validity of this assumption has been called into question (Wasserman et al. 2018). Few studies did not base their efficacy estimates for AOM on data from randomized clinical trials. Gouveia et al. (2017), for example, based their AOM efficacy estimates on observational data from the United Kingdom, which used a crude interrupted time series analysis to ascertain impact (Lau et al. 2015). Hoek, Choi, et al. (2012) assumed AOM efficacy to be a linear ratio of their estimated efficacy for IPD, based on a complex transmission dynamic model. Chuck et al. (2010) also based the efficacy for AOM on IPD, but used the observed change in invasive disease before and after vaccine introduction without any adjustments for secular trends in the pre-vaccine period. Similarly, Zhou et al. (2014) did not use any efficacy estimates, but instead directly compared published incidence rates of AOM before and after vaccine introduction, and assumed any observed difference was due to the vaccine.

The vaccine efficacy estimates for hospitalized and non-hospitalized pneumonia were generally based on S. B. Black and Shinefield (2002). As was the case for AOM, Delgleize et al. (2016) and Castiglia et al. (2017) based their pneumonia efficacy estimates on Tregnaghi et al. (2014). In the case of pneumonia, a larger proportion of studies based their estimates on either unadjusted observational studies or did not provide sufficient information to ascertain what estimates were used. Chuck et al. (2010) and Hoek, Choi, et al. (2012) again assumed the efficacy for pneumonia to be a fixed ratio of their IPD efficacy estimate. Talbird et al. (2010) and Gouveia et al. (2017) never explicitly stated their assumed vaccine efficacy, and no rationale was provided. Díez-Domingo et al. (2011) assumed a 42% efficacy against hospitalized pneumonia cases but did not provide any rationale or reference for this assumption. Zhou et al. (2014) directly compared published incidence rates for pneumonia in the pre- and post-vaccine periods, and

assumed any difference to be a direct result of vaccination. Newall et al. (2016) based the efficacy against outpatient pneumonia on S. B. Black and Shinefield (2002), as did most other studies. However, the efficacy estimates for inpatient pneumonia and IPD were determined using a novel time series methodology. They projected the rate of disease in the pre-vaccine period to the post-vaccine period using a Poisson regression model, and corrected for changes in population demographics using an offset term. With access to only three years of annual pre-vaccine incidence rates, they were unfortunately only able to correct for an intercept term, and acknowledge this in their discussion section (Newall et al. 2016). Nevertheless, the methodology is interesting. Finally, M. A. O'Brien et al. (2009) did not consider pneumonia or invasive pneumococcal disease as health outcomes.

Vaccine efficacy estimates for IPD were most often based on Black et al. (2000). One other randomized controlled trial (Palmu et al. 2013) was used by Kuhlmann and Schulenburg (2017). The remaining studies based their efficacy estimates on non-randomized or observational studies. Newall et al. (2016) used a novel regression methodology as previously described, and Chuck et al. (2010) used simple unadjusted pre- and post-vaccine observational data. Hoek, Choi, et al. (2012) utilized a complex transmission dynamic model on meticulously collected prospective surveillance data to estimate the effect of PCV13, but did not provide any reference or rationale for the efficacy parameters used in the model. Castiglia et al. (2017) assumed that the vaccine efficacy of PCV10 and PCV13 were the average of two observational studies (A. a Palmu et al. 2015; Waight et al. 2015). By et al. (2012), Delgleize et al. (2016), Knerer, Ismaila, and Pearce (2012), Newall et al. (2011) and Robberstad et al. (2011) based their efficacy estimate on a matched case-control study of PCV7, conducted in the United States in 2001-2002 (Whitney et al. 2006). Talbird et al. (2010) failed to provide any reference or rationale for their efficacy estimates.

Critical appraisals of cost-effectiveness assumptions have shown they can profoundly affect a study's outcome (Wasserman et al. 2018). The cost-effectiveness and cost-utility analyses included in this discussion based their efficacy estimates on many different studies. An alarmingly large proportion cited observational data from other time-periods and study populations, which often used a different formulation of pneumococcal conjugate vaccine. In most cases where randomized controlled trials were utilized, the most commonly referenced studies were conducted 10 years prior, in a completely vaccine naive population using PCV7. Newall et al. (2016) introduced a

thoughtful time series approach where local pre-vaccine trends in disease were statistically extrapolated to the post-vaccine period, simulating what would have occurred had the vaccine not been introduced. This was then subtracted from the observed rates of disease to estimate the true vaccine impact. However, as the authors concede in their discussion, they did not have access to adequate pre-vaccine data and were thus unable to conduct a robust statistical extrapolation (Newall et al. 2016).

The care with which the referenced efficacy data were incorporated also varied between studies. Only some considered vaccine coverage and waning vaccine protection, and few adjusted for local serotype distribution and herd effect (Table 7). Additionally, there was great variability in how the included studies defined the pre-vaccine incidence of disease, with some studies borrowing incidence estimates from other countries. A review of the epidemiological rationale used in each of the studies is beyond the scope of this thesis.

Table 7. A summary of modeling assumptions used in economic analyses of pneumococcal conjugate vaccines in high-income countries from 2009-2018. Several different modeling strategies were used, which are discussed in more detail in chapter 1.3. If the vaccine uptake was not specified this was indicated with a hyphen (-). When herd effect was included in the model, it was often only included for invasive pneumococcal disease (IPD). Serotype replacement was often only incorporated for indirect effects (herd effect). When models are based on ecological data, they implicitly include both herd effects and serotype replacement. Only Hoek, Choi, et al. (2012) directly modeled the serotype replacement. Sensitivity analyses can be either deterministic, such as 1-Way, 2-Way and scenario analyses, or stochastic, such as probabilistic sensitivity analyses (PSA) and cost-effectiveness acceptability curves (CEAC). Sensitivity analyses are discussed in more detail in chapter 1.3. The table is partially adapted from Wu et al. (2015).

Study	Model	Uptake (%)	Herd effect	Serotype replacement	Sensitivity analyses
M. A. O'Brien et al. (2009)	Markov	-	No	No	1-Way, 2-Way, threshold
Chuck et al. (2010)	Steady-state population	83.8	Yes, IPD only	No	PSA

Rozenbaum et al. (2010)	Decision analysis	-	Yes, IPD only	Yes, herd effect only	1-Way, PSA, threshold, CEAC, scenario
Rubin et al. (2010)	Markov state transition	90	Yes	Yes, ecological data	-
Talbird et al. (2010)	Steady-state population	80-91	Yes	Yes, herd effect only	1-Way, threshold
Robberstad et al. (2011)	Markov cohort	80-95	Yes, IPD only	Yes, herd effect only	1-Way, 2-Way, PSA, CEAC, scenario
Newall et al. (2011)	Markov state transition	75-95	Yes	Yes, increased incidence	1-Way, PSA, CEAC, scenario
Díez-Domingo et al. (2011)	Markov cohort	95	Yes	Yes, increased incidence	1-Way, scenario
Knerer, Ismaila, and Pearce (2012)	Markov cohort	100	Yes, IPD only	Yes, herd effect only	1-Way, PSA
Earnshaw et al. (2012)	Markov cohort	-	Yes	No	1-Way, threshold, scenario
By et al. (2012)	Markov cohort	100	Yes, IPD only	Yes, herd effect only	1-Way, scenario
Strutton et al. (2012)	Markov cohort	80-95	Yes	Yes, ecological data	1-Way, scenario
Blank and Szucs (2012)	Decision analysis	83	No	No	1-Way

Hoek, Choi, et al. (2012)	Transmission dynamic	-	Yes	Yes, directly	PSA, threshold, CEAC, scenario
Klok et al. (2013)	Markov state transition	-	Yes	Yes, ecological data	1-Way, scenario
Zhou et al. (2014)	Decision analysis	-	No	No	1-Way, scenario
Delgleize et al. (2016)	Markov cohort	100	Yes, IPD only	Yes, herd effect only	1-Way, PSA, threshold, CEAC, scenario
Newall et al. (2016)	Markov state transition	-	Yes, IPD only	Yes, ecological data	PSA, threshold, CEAC, scenario
Castiglia et al. (2017)	Markov cohort	87.46	Yes, IPD only	Yes, herd effect only	1-Way, PSA, threshold, scenario
Gouveia et al. (2017)	Markov cohort	60.8	Yes, IPD only	No	1-Way, scenario
Kuhlmann and Schulenburg (2017)	Markov state transition	90	Yes	Yes	1-Way, PSA, threshold, CEAC, scenario

### 1.3.2 Assumptions regarding costs and utilities in economic analyses of pneumococcal vaccines

Cost-utility analyses present results as the cost of an intervention per additional quality-adjusted life-years gained. QALYs are a good universal measure of benefit, provided that the quality adjustments for the included health outcomes accurately reflect the true preferences of the population for which the cost-utility analysis is informing decision making. Without this

correlation, the resulting cost-utility ratio is at best externally valid in comparison to other studies which use the same utility weights, but has no intrinsic validity to inform decision-makers. Similarly, the costs associated with each vaccine and health outcome must necessarily be derived from accurate estimates of the population under study. If costs are measured imprecisely or obtained from other countries or time-periods, it is difficult to imagine what relevance the economic analysis has to the decisions at hand.

To date, only three studies have been published that estimate utility values for pneumococcal diseases by interviewing children, or parents of children, who have experienced the disease. One study in the United States in 2001 used time trade-off and willingness-to-pay methods to estimate the utility values associated with simple and complex acute otitis media, moderate and severe pneumonia, meningitis and bacteremia (Prosser et al. 2004). Another study from the United Kingdom used the health utility index to estimate utility values for pneumococcal meningitis (Legood et al. 2009). In a French study (Andrade et al. 2018), the utility values for adult pneumococcal pneumonia were estimated using the EuroQoL five dimensional questionnaire. Two additional studies examined utility values in populations that had not experienced pneumococcal disease. Bennett et al. (2000) estimated utility values for meningitis sequelae; deafness and moderate and severe brain damage by interviewing parents of mildly sick toddlers presenting to urgent care for unrelated illnesses. Oostenbrink, A Moll, and Essink-Bot (2002) surveyed 28 pediatricians in the Netherlands using the health utility index and EuroQoL five dimensional questionnaires to ascertain utility weights for long term sequelae of bacterial meningitis.

With few exceptions, all of the reviewed cost-utility analyses used the same two references for utilities (Bennett et al. 2000; Oostenbrink, A Moll, and Essink-Bot 2002). Most of the studies did so indirectly (Kuhlmann and Schulenburg 2017; Newall et al. 2011, 2016; Rozenbaum et al. 2010; Rubin et al. 2010; Talbird et al. 2010), and instead cited a cost-utility analysis by A. Melegaro and Edmunds (2004), which itself based its estimates on the two studies. Earnshaw et al. (2012), Knerer, Ismaila, and Pearce (2012) and By et al. (2012) took the extra step of citing Morrow et al. (2007), which itself cites A. Melegaro and Edmunds (2004). This is significant, as the method A. Melegaro and Edmunds (2004) used to aggregate and translate utility values to QALYs is controversial (Herdman et al. 2016). M. A. O'Brien et al. (2009) based their utility values on Prosser et al. (2004). Klok et al. (2013) used utilities based on a Maddigan, Feeny, and Johnson (2005), which is a study of the quality of life of diabetic adults in Canada, and provided no rationale for

its relevance to pneumococcal disease in Danish and Swedish children. Strutton et al. (2012) claimed to use country specific utilities for Germany, Greece and the Netherlands, but provided no reference for the utility values, which are the same for each country and identical to those in Maddigan, Feeny, and Johnson (2005). Chuck et al. (2010) references the Canadian National Advisory Committee on Immunization statement on the recommended use of pneumococcal conjugate vaccine, which is not available online. Despite the considerable uncertainty associated with utilities, they were often not examined with sensitivity analyses (Blank and Szucs 2012; Chuck et al. 2010; Earnshaw et al. 2012; Gouveia et al. 2017; Klok et al. 2013; Newall et al. 2016; Strutton et al. 2012; Talbird et al. 2010).

Costs included in economic analyses are divided into direct and indirect costs. Direct costs include the cost of each vaccine dose, the cost of hospitalized and outpatient health outcomes, and the cost of long-term sequelae. The reviewed studies invariably used the list price of pneumococcal conjugate vaccines which were available in their respective countries at the time the cost-effectiveness analysis was undertaken. These valuations must be considered conservative estimates of the cost-effectiveness, as health care systems generally negotiate the purchase price of vaccines at a considerably lower prices than listed. Studies comparing two higher-valency pneumococcal conjugate vaccines most commonly used the list price of the available vaccine and assumed price parity. By negating the possibility of competition between the two vaccine manufacturers, the studies make an unreasonable assumption. At the very least, such assumptions call for a sensitivity analysis, which some of the reviewed studies failed to perform for any of the cost components (Chuck et al. 2010; Earnshaw et al. 2012; Gouveia et al. 2017; Klok et al. 2013; Newall et al. 2016; Strutton et al. 2012; Talbird et al. 2010).

The included studies most commonly estimated direct costs associated with hospitalized health outcomes, by utilizing official statistics of resources associated with diagnostic related groupings, and unit costs derived from national tariffs. Expert opinion was then sought to decide which resources on average, would be used for each health outcome. With this input, a hypothetical reference case was constructed and used to calculate the direct cost. Outpatient health outcomes were often solely based on the assumptions of expert opinion, with the exception of studies conducted in the Netherlands, Germany and the United Kingdom, where official statistics on outpatient unit costs are available. The basis of what was considered expert opinion was stated in only one case (Knerer, Ismaila, and Pearce 2012). This

practice sometimes resulted in suspect estimates, for example, that in Greece, each case of outpatient AOM cost 3,861 euros which was 30-300 times higher than for the two other countries included in the study (Strutton et al. 2012). This is particularly unfortunate as costs were not included in the sensitivity analysis in that study. Díez-Domingo et al. (2011) and Hoek, Choi, et al. (2012) obtained average costs and hospital length of stay for each health condition directly from medical records. The direct cost of long-term sequelae was, with few exceptions, based on assumptions and expert opinion.

Indirect costs mainly compromises lost workdays, and were only included in few of the reviewed studies (By et al. 2012; Delgleize et al. 2016; Gouveia et al. 2017; Kuhlmann and Schulenburg 2017; Robberstad et al. 2011; Rozenbaum et al. 2010). M. A. O'Brien et al. (2009) included parental time spent for outpatient visit, but not lost workdays. Generally, average wage and unemployment rates were extracted from official statistics, and multiplied by the days of work lost, to estimate the indirect cost. The days of work lost were assumed to be equal to the length of hospital stay in hospitalized cases, for both adults and parents of admitted children. The days of work lost for outpatient cases were assumed to be half of that of hospitalized cases. In the case of outpatient AOM, parents were assumed to lose from zero to three days depending on the study, with no rationale provided in most studies.

In conclusion, a plethora of cost-effectiveness analyses of pneumococcal conjugate vaccines have already been published. These studies have many strengths and utilized the available data well. However, a thorough review identified several areas that could be improved upon to better inform policy decisions. Only one post-implementation cost-effectiveness study was identified, which did not have access to sufficient data to adjust the analysis for observed post-vaccine effects (Newall et al. 2016). The reviewed studies generally based their efficacy on the results of randomized controlled trials, but other parameters were variably measured. Important assumptions were regularly omitted due to the paucity of available data, such as the degree of vaccine uptake, waning protection, coverage with regard to the local serotype distribution, and the existence and extent of herd-effect and serotype-replacement. When included, they were often sourced from studies conducted in different populations. For example, all of the reviewed studies included indirect estimates of utility that were derived from studies conducted a decade prior in other populations. This is notable as utility values are meant to represent the preferences of the population being studied. Because of the inherent uncertainty of cost-effectiveness analyses, robust sensitivity

analyses are required. Probabilistic sensitivity analyses were generally well conducted, but were performed by less than half of the reviewed studies and did not always include all relevant parameters. The above identifies a role for a careful post-implementation cost-effectiveness analysis in which all parameters are measured in the population under study, and the results are examined with a probabilistic sensitivity analysis.

## **2 Aims**

The aims of the thesis were to estimate the impact of PHiD-CV10 on

- i. The incidence of pediatric emergency department visits for otitis media with treatment failure (Paper I)
- ii. The population-based incidence of otitis media visits in primary care (Papers II and VI)
- iii. The population-based herd-effect on otitis media among unvaccinated children (Papers II and VI)
- iv. The population-based incidence of outpatient antimicrobial prescriptions (Paper III)
- v. The population-based incidence of tympanostomy tube procedures (Paper IV)
- vi. The population-based incidence of hospitalizations for respiratory and invasive infections commonly associated with *Streptococcus pneumoniae* (Paper V)
- vii. The population-based herd-effect on pneumonia hospitalizations among unvaccinated children and adults (Paper VI)
- viii. The population-based herd-effect on hospitalizations for invasive pneumococcal disease among unvaccinated children and adults (Paper VI)
- ix. The cost-effectiveness of introducing PHiD-CV10 into the pediatric vaccination program in Iceland (Paper VI)

### **3 Materials and methods**

#### **3.1 Data collection and sources**

During the study period from 1 January 2005 to 31 December 2017, data were collected from multiple whole population registries, and from the patient registry of Landspítali University Hospital. Data were collected based on government issued national identification numbers. Each individual receives only one number over the course of their lifetime, and the identification number is permanently retired at the time of death. The Icelandic Directorate of Health processed and anonymized all data from the various registries before releasing it to the study group. A study identifier was created based on the national identification number, which was then removed from the data as part of the anonymization process. The mapping key was kept by the Directorate of Health, and was not accessible to the study group. The study group linked data from the various registries using both the study identifier and dates of events.

In the following sub-chapters, each registry providing study data is reviewed. Statistics Iceland provided data on immigration and emigration, demographic indices and salaries. Diagnostic data were obtained from Landspítali University Hospital's patient registry and the Primary Care Registry of the Directorate of Health. Pneumococcal vaccination status was collected from the National Vaccine Registry (NVR) and augmented with information on privately purchased vaccine doses obtained from the National Drug Prescription Registry (NDPR). Data regarding antimicrobial prescriptions were also extracted from the NDPR. Finally, reimbursement data for outpatient otolaryngological procedures were obtained from Icelandic Health Insurance.

##### **3.1.1 Statistics Iceland**

Statistics Iceland collects and maintains a large array of economic, social and demographic indices, and provides aggregate data at [www.statice.is](http://www.statice.is). For each calendar-year 2005-2017, the number of individuals living in Iceland was collected from Statistics Iceland, stratified by postal-code, gender and age in years. These data were used for the denominator in incidence calculations in all papers. The deciles of salary from 2005-2017 were obtained from Statistics Iceland and used to inform a sensitivity analysis on the cost-effectiveness of PHiD-CV10 ( Paper VI). Costs were adjusted for inflation using the Medical Care Consumer Price Index of Statistics Iceland, and wages adjusted using the National Wage Index. In addition to the

aggregate data presented above, individual-level information on the immigration and emigration of children zero to four years of age was obtained, anonymized and linked to the other study data.

### **3.1.2 Landspítal University Hospital patient registry**

Landspítal University Hospital is the sole tertiary hospital in Iceland, and includes Children's Hospital Iceland – Iceland's only pediatric hospital. It provides primary and secondary care for the capital area, approximately 65% of the Icelandic population, and tertiary care for the whole population. In 2017, the total number of non-psychiatric curative care hospital beds in Iceland was 732 ([www.statice.is](http://www.statice.is)). Of those, 669 (91%) were at Landspítal University Hospital. Landspítal's patient registry records information on all emergency department and outpatient visits, and all hospital admissions to Landspítal University Hospital. For the period from 1 January 2005 to 31 December 2017, data were extracted on all unplanned acute-care visits and hospital admissions with International Classification of Diseases, 10th revision (ICD-10) discharge diagnoses compatible with respiratory infections (Table 8).

Table 8. The International Classification of Diseases, 10th revision (ICD-10) codes used for individual-level data collection from the Primary Care Registry and Landspítal University Hospital's patient registry. All subgroups of the listed ICD-10 codes were also included.

ICD-10 code	Disease
A40	Streptococcal sepsis
A41	Other sepsis
A48	Other bacterial diseases, not elsewhere classified
A49	Bacterial infection of unspecified site
B00	Herpesviral [herpes simplex] infections
B08	Other viral infections characterized by skin and mucous membrane lesions, not elsewhere classified
B33	Other viral diseases, not elsewhere classified
B34	Viral infection of unspecified site
B95	Streptococcus, Staphylococcus, and Enterococcus as the cause of diseases classified elsewhere

B96	Other bacterial agents as the cause of diseases classified elsewhere
G00	Bacterial meningitis, not elsewhere classified
H65	Nonsuppurative otitis media
H66	Suppurative and unspecified otitis media
H70	Mastoiditis and related conditions
H72	Perforation of tympanic membrane
H73	Other disorders of tympanic membrane
J00	Acute nasopharyngitis [common cold]
J01	Acute sinusitis
J02	Acute pharyngitis
J03	Acute tonsillitis
J04	Acute laryngitis and tracheitis
J05	Acute obstructive laryngitis [croup] and epiglottitis
J06	Acute upper respiratory infections of multiple and unspecified sites
J09	Influenza due to certain identified influenza viruses
J10	Influenza due to other identified influenza virus
J11	Influenza due to unidentified influenza virus
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Hemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere
J18	Pneumonia, unspecified organism
J20	Acute bronchitis
J21	Acute bronchiolitis
J22	Unspecified acute lower respiratory infection
J32	Chronic sinusitis
J36	Peritonsillar abscess

J40	Bronchitis, not specified as acute or chronic
J85	Abscess of lung and mediastinum
J86	Pyothorax
J90	Pleural effusion, not elsewhere classified
N30	Cystitis
N39	Other disorders of urinary system
R05	Cough
R50	Fever of other and unknown origin

Additionally, any visit or hospital admission associated with NOMESCO Classification of Surgical Procedures (NCSP) procedural codes in Table 9 were extracted the patient registry.

Table 9. NOMESCO Classification of Surgical Procedures (NCSP) codes used for individual-level data collection from Landspítali University Hospital's patient registry.

NCSP code	Description
EMSB00	Excision of lesion of tonsil or adenoid
EMSB10	Tonsillectomy
EMSB15	Intracapsular destruction of tonsils
EMSB20	Adenotonsillectomy
EMSB30	Adenectomy
EMSB99	Other excision on tonsils and adenoids
EMSW99	Other operation on tonsil or adenoids
DCSA10	Paracentesis of tympanic membrane
DCSA20	Insertion of ventilating tube through tympanic membrane
DCSW00	Removal of ventilating tube from tympanic membrane

The data included the date of visit or hospital admission, date of hospital discharge, hospital length of stay, the departments involved (including the intensive care unit), and a detailed breakdown of costs associated with each contact. A separate and unique identification number was provided for each individual visit or hospital admission. All costs were recorded in Icelandic kronas (ISK) and were broken down into specific subsets. Costs associated with diagnostic testing were provided and categorized as costs associated

with chemical blood testing; diagnostic radiological testing; anatomical pathology; virological testing; bacteriological cultures; antibody and other immunological testing; and specific tests performed by the blood bank in preparation for the administration of blood products. Costs associated with departmental upkeep, such as heat, electricity, and wages were divided between patients based on hospital length of stay. The costs associated with treatment were divided into the cost of drugs, surgery and procedures and intensive care unit treatment.

Several smaller independent data-sets pertaining to specific papers were extracted from the patient registry. These data-sets were not linked to the main study data.

In paper I, describing the impact of PHiD-CV10 on acute otitis media with treatment failure, information on all doses of ceftriaxone administered at the Children's Hospital Iceland between January 2009 and December 2015 was extracted from the hospital's medication administration system using the ATC code J01DD0. Any ICD-10 diagnostic code associated with a visit or hospital admission in which ceftriaxone was administered, was extracted from the patient registry. Importantly, this included all ICD-10 codes, not only those in Table 8. Also obtained for paper I was the aggregate number of yearly visits to the pediatric emergency department of Children's Hospital Iceland 2008-2015.

Paper VI – a cost-effectiveness analysis of PHiD-CV10 introduction into the pediatric vaccination program, required control diseases used within a time series analysis framework. The aggregate monthly number of acute-care visits and hospital admissions for several sub-chapters of the ICD-10 diagnostic coding system (Table 10) was obtained for 22 different age-groups.

Table 10. The International Classification of Diseases, 10th revision subchapters used to define the synthetic controls used in time series analyses.

ICD-10 code	Description
A10-B99	Certain infectious and parasitic diseases
C00-D48	Neoplasms
D50-89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism

E00-99	Endocrine, nutritional and metabolic diseases
G00-G99	Diseases of the nervous system
H00-99	Diseases of the eye and adnexa, Diseases of the ear and mastoid process
I00-99	Diseases of the circulatory system
K00-99	Diseases of the digestive system
L00-99	Diseases of the skin and subcutaneous tissue
M00-99	Diseases of the musculoskeletal system and connective tissue
N00-99	Diseases of the genitourinary system
P00-99	Certain conditions originating in the perinatal period
Q00-99	Congenital malformations, deformations and chromosomal abnormalities
R00-99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
S00-T99	Provisional assignment of new diseases of uncertain etiology
U00-99	Injury, poisoning and certain other consequences of external causes
V00-Y99	External causes of morbidity
Z00-99	Factors influencing health status and contact with health services

Data from the patient registry were used in paper I, paper IV, paper V and paper VI.

### 3.1.3 The Primary Care Registry

In the Icelandic health care system, primary care is provided by family medicine physicians at 69 neighborhood based centers (*Heilsugæsla*). All primary care centers use the same electronic medical record system, and the same diagnostic coding systems (NCSP, ICD-10) as Landspítali University Hospital and Children's Hospital Iceland. The Directorate of Health maintains a registry on all primary care visits within the Icelandic health care system. From this registry, all physician visits with ICD-10 diagnostic codes compatible with respiratory tract infections were extracted for the period 1 January 2005 to 31 December 2015 (Table 8). From early 2016, extensive maintenance and restructuring of the registry has been ongoing, and no new data have been added since 31 December 2015.

Data from the Primary Care Registry were used in paper II, paper III, paper IV and paper VI.

### **3.1.4 The National Vaccine Registry**

The Icelandic Directorate of Health also maintains the National Vaccine Registry (NVR). All vaccine doses administered within the health care system are systematically recorded in an individual's electronic health record at the time they are administered. This record is reviewed and updated regularly, and vaccinations given in other health care facilities are included. The NVR collects this information from all electronic health records in the country. Vaccines are categorized using the Anatomical-Therapeutic-Chemical (ATC) classification system of the World Health Organization. All administered vaccine doses with ATC codes "J07AL" (Pneumococcal vaccines) were extracted for the period of 1 January 2005 to 31 December 2017.

Data from the NVR were used in all papers.

### **3.1.5 The National Drug Prescription Registry**

The national drug prescription registry (NDPR) is a whole-population registry, collected and maintained by the Icelandic Directorate of Health since 1 January 2005. It contains information on all filled drug prescriptions in Iceland. All pharmacies are required by law to collect data on each filled prescription and submit them to the NDPR. An important distinction must be made between a written prescription and a filled prescription. The NDPR receives information if and when a prescription is filled. It does not record information on written prescriptions that were never filled by the patient. Therefore, all prescriptions documented within the NDPR were paid for and received by the patient. Extensive validation and error testing have been performed by the Directorate of Health to ensure the robustness of the NDPR. Automated electronic submissions, coupled with tightly controlled processes by which pharmacies dispense drugs, has essentially excluded the possibility of any filled prescriptions escaping registration.

All prescriptions within the ATC therapeutic subgroup "J01" (Antibacterials for Systemic Use), "J07" (Vaccines), "S01" (Ophthalmologicals) and "S02" (Otologicals) were extracted for the period from 1 January 2005 to 31 December 2017. The chemical levels used in the study are shown in Table 11

Table 11. Anatomical Therapeutic Chemical (ATC) codes used for individual-level data collection from the National Drug Prescription Registry. ATC codes are presented down to the therapeutic level, and all sublevels of the listed ATC codes

were also included. ATC codes J07 and sublevels were used to extract data on pneumococcal vaccine doses from the National Vaccine Registry.

ATC chemical subgroup code	Description
J01A	Tetracyclines
J01B	Amphenicols
J01C	Beta-lactam antibacterials, penicillins
J01D	Other beta-lactam antibacterials
J01E	Sulfonamides and trimethoprim
J01F	Macrolides, lincosamides and streptogramins
J01G	Aminoglycoside antibacterials
J01M	Quinolone antibacterials
J01R	Combinations of antibacterials
J01X	Other antibacterials
J07A	Bacterial vaccines
J07B	Viral vaccines
J07C	Bacterial and viral vaccines
J07X	Other vaccines
S01A, S02A	Anti-infectives
S01C, S02C	Anti-inflammatory agents and anti-infectives in combination

Data from the NDPR were used in paper II, paper III and paper IV.

### 3.1.6 Reimbursement database of Icelandic Health Insurance

The health care system in Iceland is a single-payer system with one government-run health insurance provider, under which all permanent citizens are covered. Most health care visits require a nominal out-of-pocket fee, with the rest of the visit covered by the insurance. There are exceptions to this – for example, visits by children under two years of age are completely covered by insurance. Health care providers are either salaried governmental employees, or independent practitioners who are reimbursed on a per case basis, according to pre-determined negotiations with Icelandic Health Insurance. To receive pay for services, physicians must submit a reimbursement form, detailing the nature of the visit and any procedures

performed using pre-specified procedural codes. Icelandic Health Insurance maintains a reimbursement database which details the nature and number of procedures performed. Data on all otolaryngological procedures performed on the middle ear and tonsils were extracted from the reimbursement database for the period from 1 January 2005 to 31 December 2017 using the procedural codes in Table 12

Table 12. Reimbursement codes used for individual-level data collection from the Reimbursement database of Icelandic Health Insurance. The codes are specific to Icelandic Health Insurance and do not represent a universal classification system. With one exception (Myringotomy, one or both ears, under local anesthetic), each reimbursable procedure has three associated reimbursement codes. One general (without letters), one specifically for surgeons (Z) and one specifically for anesthesiologists (Q).

Reimbursement code	Description
5500601	Myringotomy, one or both ears, under local anesthetic
5500602/55Q0602+55Z0602	Placement of tympanostomy, one ear (local anesthetic/general anesthesia)
5500603/55Q0603+55Z0603	Placement of tympanostomy tube, one ear, and myringotomy, both ears (local anesthetic/general anesthesia)
5500604/55Q0604+55Z0604	Removal of tympanostomy tube, one ear (local anesthetic/general anesthesia)
5501001/55Q1001+55Z1001	Placement of tympanostomy tube, both ears (local anesthetic/general anesthesia)
5501002/55Q1002+55Z1002	Removal of tympanostomy tube, both ears (local anesthetic/general anesthesia)
5501201/55Q1201+55Z1201	Adenoideectomy (local anesthetic/general anesthesia)
5501301/55Q1301+55Z1301	Adenoideectomy and placement of tympanostomy tube or myringotomy, one or both ears (local anesthetic/general anesthesia)
5501801/55Q1801+55Z1801	Tonsillectomy with or without adenoideectomy (local anesthetic/general anesthesia)

5501802/55Q1802+55Z1802	Tonsillectomy with or without adenoidectomy - performed with laser (local anesthetic/general anesthesia)
5501901/55Q1901+55Z1901	Tonsillectomy, with or without adenoidectomy, and tympanostomy or myringotomy (local anesthetic/general anesthesia)
5501902/55Q1902+55Z1902	Tonsillectomy, with or without adenoidectomy, and tympanostomy or myringotomy - performed with laser (local anesthetic/general anesthesia)
5502002/55Q2002+55Z2002	Myringoplasty with patch (local anesthetic/general anesthesia)

Data from the reimbursement database were used in paper IV.

### 3.2 Impact on otitis media with treatment failure (Paper I)

The objective of Paper I was to evaluate whether the introduction of PHiD-CV10 was associated with a reduction in the incidence of otitis media with treatment failure. Treatment of otitis media with ceftriaxone was used as a proxy for treatment failure. Ceftriaxone use for other diagnoses and in older children was used as a comparator.

All children under 18 years of age who visited Children's Hospital Iceland between 1 January 2008 and 31 December 2015 were included. Children's Hospital Iceland's referral area was defined as a 100 kilometer driving distance from the hospital. Population demographic data for the referral area were obtained from Statistics Iceland ([www.statice.is](http://www.statice.is)), as previously described in 3.1.1.

Data were extracted from Landspítali University Hospital's patient registry. A visit was included in the study if an ICD-10 code of Nonsuppurative otitis media (H65) or Suppurative and unspecified otitis media (H66) was documented in the medical record, or if a child received one or more doses of ceftriaxone. All administered doses of ceftriaxone were systematically extracted from the hospital's medication administration system using the ATC code J01DD04. The ICD-10 diagnoses associated with the ceftriaxone administrations were then obtained from the patient registry. The total number of visits per calendar year and month regardless of diagnosis was provided by the hospital.

Pre-vaccine (2008-2011) and post-vaccine (2012-2015) periods were defined based on the year of vaccine introduction. Because hospital visits for otitis media (OM) are uncommon in older children, the primary analysis was restricted to children under four years of age. Ceftriaxone use was analyzed in three separate diagnostic groups; otitis media, pneumonia, and other, based on the associated ICD-10 diagnostic codes. Ceftriaxone was considered to be due to OM, if an ICD-10 code of Nonsuppurative otitis media (H65) or Suppurative and unspecified otitis media (H66) was recorded. It was considered due to pneumonia if ICD-10 codes Bacterial pneumonia, not elsewhere classified (J15) or Pneumonia, unspecified organism (J18) was recorded. Visits associated with ceftriaxone administration that did not fall into either of the above categories were classified together as "Other".

The number of ceftriaxone treatment episodes per diagnostic group was aggregated by calendar month. An episode was considered distinct if no ceftriaxone administration was documented in the previous 14 days. Incidence rates (IR) per 1,000 person-years were calculated by dividing the monthly number of ceftriaxone episodes per diagnostic group by the number of person-years accrued by children in the referral area. The IR of OM visits were similarly defined and calculated. If a decrease were to be observed in the number of ceftriaxone treated OM episodes, it could be due to either a decrease in the number of OM visits or a decrease in the use of ceftriaxone. To evaluate this, the incidence risk of ceftriaxone treated OM episodes was calculated per 1,000 OM episodes presenting to Children's Hospital Iceland for both the pre- and post-vaccine periods.

Statistical analysis was performed in R version 3.4.4. (R Core Team 2019) using the epiR package (Stevenson et al. 2018). Incidence rate ratios ( $IRR$ ) were calculated between the pre- and post-vaccine periods, and were estimated independently for each age-strata. The stratum-specific estimates were combined (when appropriate) using the Mantel-Haenszel method and 95% confidence intervals (CI) calculated using the delta procedure (Kirkwood and Sterne 2003). The Mantel-Haenszel estimate of the incidence rate ratio ( $IRR_{MH}$ ) is the weighted mean of the  $IRR$  in each stratum. The null-hypothesis that  $IRR_{MH} = 1$  was tested by calculating the Mantel-Haenszel  $\chi^2$  test statistic, from which the  $P$ -value was derived.

Combining stratum-specific estimates is appropriate when the exposure-outcome association is the same in each of the strata, i.e.  $IRR_{age} = IRR_{MH}$ . The  $\chi^2$  test of heterogeneity assesses whether the data is congruent with the null hypothesis which predicts no effect modification of the exposure-outcome

relationship by strata. The greater the differences are between  $IRR_{age}$  and  $IRR_{MH}$ , the larger the  $\chi^2$  statistic. If the null hypothesis is rejected, the  $IRR_{MH}$  is not calculated and only the stratum-specific  $IRR$  are presented.

### 3.3 Impact on primary care visits for acute otitis media (Paper II)

The objective of Paper II was to evaluate the impact of PHiD-CV10 on the incidence of acute otitis media in Icelandic children. Paper II is a population-based observational cohort study that followed all children born in Iceland between 1 January 2005 and 31 December 2015, from birth until three years of age, death or end of the study period. All primary care visits in which an ICD-10 diagnostic code of suppurative otitis media (H66) was recorded were included. Any visits occurring within 30 days of a previously documented visit by the same child were excluded from the main analysis. The study therefore represented AOM episodes, rather than AOM visits.

Data were obtained from the Primary Care Registry of the Icelandic Directorate of Health. In addition to the diagnosis of acute otitis media, the data included all ICD-10 codes associated with the visit, as well as the date of the visit, age and gender of the child, and physician identification number. The study identification number used to identify unique individuals is derived from the national identification numbers issued to individuals by the government. Those who had immigrated to Iceland after birth were excluded. Demographic population data was obtained from Statistics Iceland.

Cohorts were defined based on year of birth or vaccine eligibility. Birth-cohorts 2005–2010 were grouped as vaccine non-eligible cohorts (VNEC) and birth-cohorts 2011–2015 as vaccine eligible cohorts (VEC). Statistical analyses were performed in R version 3.4.4. (R Core Team 2019) using the R packages; survival (Therneau 2018), RMS (Harrell, Jr. 2019) and epiR (Stevenson et al. 2018).

Crude incidence rates of AOM visits were calculated per 100 person-years at risk for each birth cohort, stratified by four-month age brackets. Following each AOM visit, there was a 30 day period in which it was impossible for a visit to be recorded due to the study design. To avoid misclassifying this period, the individual time at-risk was carefully constructed to exclude the 30 days following each recorded otitis media visit. Crude incidence rate ratio between VNEC and VEC were calculated and confidence intervals estimated assuming Poisson variance.

In the subset of children who had full follow-up time, the number of children who cumulatively experienced 0-12 episodes of AOM were tabulated, and the distribution between VNEC and VEC compared using the  $\chi^2$  test of homogeneity. Additionally, the crude risk ratio between the VEC and VNEC of experiencing 0, 1–4, or >5 episodes of AOM before three years of age was calculated.

The Andersen-Gill extension of the Cox regression model for repeated events was used to model data on the individual-level and to account for censoring of follow-up time (Andersen and Gill 1982). To correct for successive visits by the same individual, Lin and Wei (1989) sandwich variance estimates were used. From this model, the hazard ratio (HR) of AOM visits between each birth-cohort and the last vaccine non-eligible cohort was calculated. The impact of PHiD-CV10 on AOM visits was defined as  $1 - (HR \text{ between the last vaccine-eligible birth cohort and the last vaccine non-eligible cohort}) * 100\%$ .

The HR between VNEC and VEC was calculated for each number of previous AOM visits, and the mean number of episodes as a function of age was estimated from the model using the generalized Nelson-Aalen estimator (Cook and Lawless 2007). To determine the number of AOM episodes prevented in the first five years of the vaccination, each child's follow-up time was multiplied by the Nelson-Aalen estimate of the mean number of episodes. The absolute reduction in the IR was then calculated by dividing the estimated number of prevented episodes with the total person-time of the VEC.

### **3.4 Impact on outpatient antimicrobial prescriptions (Paper III)**

The objective of Paper III was to estimate the impact of PHiD-CV10 on outpatient antimicrobial prescriptions among children in Iceland. Paper III is a population-based observational cohort study of antimicrobial prescriptions in children under three years of age in Iceland. Eleven consecutive Icelandic birth-cohorts 2005–2015 were followed from birth until three years of age. Children who immigrated to Iceland after birth were excluded. Follow-up time was censored on death, emigration, or the end of the study period (31 December 2016). Because of shortened follow-up time, the 2016 birth-cohort was not included in the analysis.

Data regarding outpatient antimicrobial prescriptions were obtained from the National Drug Prescription Registry, as previously described in 3.1.5.

Data on primary care visits for respiratory tract infections were collected from the Primary Care Registry using the ICD-10 codes in Table 8. Prescriptions filled within three days of a documented physician visit by the same child were linked. Because data from the Primary Care Registry was only available through 31 December 2015, the portion of the analysis pertaining to the linked data was restricted to that date. Demographic population data were acquired from Statistics Iceland (<https://www.statice.is/>).

Data was analyzed both descriptively and from a cohort perspective. Descriptive analysis included all Icelandic children under three years of age during the study period. Statistical analyses were performed in R version 3.4.4. (R Core Team 2019) using the R packages survival (Therneau 2018), RMS (Harrell, Jr. 2019) and epiR (Stevenson et al. 2018). Based on a previously published study, all filled antimicrobial prescriptions were classified into one of six categories; first and second line penicillins, first and second generation macrolides, cephalosporins, and finally, others (Youngster et al. 2017). The proportion of prescriptions within each category was calculated by calendar-year. Five diagnostic-groups were defined, based on primary care ICD-10 diagnoses, and the proportion of cases resulting in an antimicrobial prescription was calculated per calendar-year. The five diagnostic-groups were; Acute upper respiratory infections (J00-J06), Influenza and pneumonia (J09-J18), Other acute lower respiratory infections (J20-J22), AOM (H65, H66 and H72) and Other viral infections (B34).

Birth-cohorts were compared either individually, or grouped by vaccine eligibility. In the individual birth-cohort analysis, each birth-cohort was compared to the last vaccine non-eligible cohort, i.e. the 2010 birth-cohort. Birth-cohorts 2011–2015 were grouped as vaccine-eligible cohorts (VEC), and birth-cohorts 2005–2010 as vaccine non-eligible cohorts (VNEC). The incidence rate (*IR*) of antimicrobial prescriptions per 100 person-years was calculated in six-month age-brackets for each birth-cohort. Ninety-five percent confidence intervals were estimated using the Wald method (Kirkwood and Sterne 2003). Incidence rate ratios (*IRR*) between the VNEC and the VEC were estimated, and 95% confidence intervals calculated assuming Poisson variance. The cumulative proportion of children who had filled at least one antimicrobial prescription by three years of age, was calculated and compared between the VEC and VNEC using the  $\chi^2$  test of homogeneity. The cumulative number of prescriptions by three years of age per child, was categorized as <1, 1–4, 5–9, 10–14 and  $\geq 15$  prescriptions. The ratio between VNEC and VEC was then calculated for each of these

categories. The 2014 and 2015-cohorts were excluded from the cumulative analyses, as they did not have the full three-year follow-up time.

The Andersen-Gill time-to-event model was fitted to the individual-level data (Andersen and Gill 1982). It was used to estimate the hazard ratio (HR) of antimicrobial prescription between the study birth-cohorts, which were included in the model as a categorical variable. Age was accounted for by defining it as the model's underlying measurement of time. The model was stratified by gender to allow for independent baseline hazards. The number of previous antimicrobial prescriptions was included in the model, and its effect allowed to be non-linear by means of restricted cubic splines (Cook and Lawless 2007). Lin and Wei (1989) robust sandwich variance estimates were applied to account for the correlation between successive prescriptions filled by the same child.

The impact of PHiD-CV10 on outpatient antimicrobial prescriptions was estimated as  $1 - (\text{the hazard ratio between the last vaccine eligible and last vaccine non-eligible cohort}) * 100\%$ . The impact on each successive prescription was also estimated. Finally, the generalized Nelson-Aalen estimate of the mean number of antimicrobial prescriptions for each gender and vaccine-cohort was calculated (Cook and Lawless 2007). To estimate the absolute number of prevented antimicrobial prescriptions during the first seven years of the intervention, the following formula was utilized; first, the expected number of prescriptions per child was added together by multiplying each child's follow-up time with the VNEC estimate of the mean number of prescriptions per child. Next, the expected number of prescriptions per child was estimated using the VEC estimate of the mean. Finally, the absolute number prevented was calculated by subtracting the VEC total from the VNEC total. The absolute rate reduction was then calculated by dividing the absolute number prevented, with the number of person-years at-risk in the VEC.

A sub-analysis was performed to estimate the vaccine impact against OM-associated antimicrobial prescriptions. The above described regression methodology was applied to those antimicrobial prescriptions that were linked to a primary care physician visit resulting in a diagnosis of AOM.

### **3.5 Impact on tympanostomy tube procedures (Paper IV)**

The objective of Paper IV was to estimate the impact of PHiD-CV10 on the incidence of tympanostomy tube placements (TTP) among children in Iceland. Paper IV is an individual-level observational cohort study of all

outpatient TTP procedures in Iceland. The study period is from 1 January 2005 to 31 December 2016. Eleven consecutive birth-cohorts 2005-2015, were followed from birth until five years of age, or end of the study period. Children who immigrated to Iceland after birth were excluded from the analysis. Those children who emigrated were censored from the study on the date of emigration. This allowed for accurate person-year at risk calculations.

Data on outpatient TTP was obtained from the Icelandic Health Insurance reimbursement database, using reimbursement codes compatible with TTP (Table 12). Information regarding inpatient TTP was extracted from Landspítali University Hospital's patient registry using NCSP codes (Table 9). These data were linked with data on primary care and emergency department visits for otitis media (OM). Data on primary care visits were obtained from the Primary Care Registry, and information regarding emergency department visits was extracted from the hospital's patient registry. Primary care data were only available until 31 December 2015. A visit was considered to be due to OM if an ICD-10 diagnostic code of Non-suppurative otitis media (H65), Suppurative otitis media (H66), Mastoiditis (H70) or Perforation of tympanic membrane (H72) was recorded. A repeat visit within 30 days was assumed to represent the same episode, and was excluded. Data regarding filled antimicrobial prescriptions were extracted from the National Drug Prescription Registry using ATC code J01 (antibacterials for systemic use).

Cohorts were defined based on year of birth or vaccine eligibility. Birth-cohorts 2005-2010 were classified as vaccine non-eligible cohorts (VNEC) and birth-cohorts 2011-2015 as vaccine-eligible cohorts (VEC). Statistical analyses were performed in R version 3.4.4. (R Core Team 2019) using the R packages; survival (Therneau 2018), RMS (Harrell, Jr. 2019) and epiR (Stevenson et al. 2018). Crude incidence rates (IR) of TTP per 100 person-years were calculated for each birth-cohort in 6-month age-groups. Crude incidence rate ratios (IRR) between the VEC and VNEC were calculated, and 95% confidence intervals estimated assuming Poisson variance. The Kaplan-Meier product limit estimate was used to calculate the cumulative proportion of TTP procedures for each birth-cohort, and confidence intervals calculated using the log delta method.

The comparison of the risk of TTP between birth-cohorts was adjusted for two confounders; the number of prior OM diagnoses and the number of prior antimicrobial prescriptions. Among children who had undergone TTP and had the full five year follow-up time, the distribution in the number of previous

visits and prescriptions was compared between VNEC and VEC using the  $\chi^2$  test of independence. When adjusting for the number of previous visits, four years was considered full follow-up time due to restricted data. If a significant difference was detected, the risk ratio and absolute risk difference between VEC and VNEC were calculated, stratified by the prior number of visits or antimicrobial prescriptions. Confidence intervals were estimated with the  $\chi^2$  of independence.

A Cox regression model was constructed to accurately account for the influence of age and censored follow-up time. Three separate models were estimated. The first did not adjust for prior OM visits or antimicrobial prescriptions, while the latter two did. The Cox regression model using the number of previous OM visits was censored at 31 December 2015 due to restricted data. Each Cox model was stratified by gender. Correlation between repeated observations of the same child was adjusted using Lin and Wei (1989) sandwich variance estimates. The hazard ratio (HR) of TTP was estimated between each of the study's birth-cohorts. The vaccine impact of PHiD-CV against TTP was estimated as 1 – (the hazard ratio between the last vaccine eligible cohort and the last vaccine non-eligible cohort) \* 100%.

### **3.6 Impact on respiratory associated hospitalizations (Paper V)**

The objective of Paper V was to estimate the impact of PHiD-CV10 on the incidence of pediatric hospitalizations due to diseases commonly caused by *Streptococcus pneumoniae*. Paper V is a single-center, individual-level, observational cohort study of pediatric hospitalizations. Eleven consecutive Icelandic birth-cohorts 2005–2015 were followed from birth until three years of age. Immigration and emigration data obtained from Statistics Iceland was used to exclude children who had immigrated to Iceland after birth. Included were all hospital admissions to the Children's Hospital Iceland 1 January 2005 to 31 December 2016. The Children's Hospital Iceland is the primary pediatric hospital for approximately 90% of Iceland's population ([www.statice.is](http://www.statice.is)), and serves as a secondary and tertiary pediatric hospital for the entire country. Data on admissions were collected from Landspítali University Hospital's patient registry. Microbiological data were extracted from a database maintained by the Department of Clinical Microbiology at Landspítali University Hospital.

Seven diagnostic groups were defined in this paper. Five of these represent diseases commonly caused by *Streptococcus pneumoniae*; Invasive pneumococcal disease (IPD), meningitis, sepsis, pneumonia and

otitis media. The remaining two groups, upper respiratory tract infections (URTI) and other lower respiratory tract infections (LRTI), were included as comparators. Hospitalization was categorized in a diagnostic group, if the relevant ICD-10 diagnostic code was recorded on the discharge chart, or if the admission was associated with microbiologically-confirmed IPD. Admissions with ICD-10 discharge diagnoses compatible with meningitis (G00) were grouped as meningitis. Those with A40 or A41 diagnoses were grouped as sepsis; with J09-J18, as pneumonia; J20-J22 as LRTI; H65, H66, H70 and H72 as OM; and J01-J06 as URTI (Table 13). A hospitalization was considered to be due to IPD if associated with culture or PCR confirmed *Streptococcus pneumoniae* sampled from joint fluid, bone, cerebrospinal fluid or blood, regardless of ICD-10 discharge diagnosis.

Table 13. Definitions of the Paper V's diagnostic groupings.

Diagnostic group	Abbreviation	Definition
Meningitis	-	ICD-10 discharge diagnosis of G00
Sepsis	-	ICD-10 discharge diagnosis of A41 or A42
Pneumonia	-	ICD-10 discharge diagnosis of J09-J18
Otitis media and complications	OM	ICD-10 discharge diagnosis of H65, H66, H70 or H72
Acute upper respiratory tract infections	URTI	ICD-10 discharge diagnosis of J00-J06
Acute lower respiratory tract infections	LRTI	ICD-10 discharge diagnosis of J20-J22
Invasive pneumococcal disease	IPD	Microbiologically confirmed pneumococcal infection from normally sterile site, regardless of ICD-10 diagnosis

Birth-cohorts were compared either individually, or grouped by vaccine eligibility. In the individual birth-cohort analysis, each birth-cohort was compared to the last vaccine non-eligible cohort, i.e. the 2010 birth-cohort. Birth-cohorts 2011–2015 were grouped as vaccine-eligible cohorts (VEC), and birth-cohorts 2005–2010 as vaccine non-eligible cohorts (VNEC). Statistical analyses were performed in R version 3.4.4. (R Core Team 2019)

using the R packages; survival (Therneau 2018), RMS (Harrell, Jr. 2019) and epiR (Stevenson et al. 2018).

Mean age at hospitalization was calculated for each birth-cohort and diagnostic group. Analysis of variance was used to test whether significant difference existed between cohorts. If an overall difference was identified, the analysis was followed by Tukey's honest significant difference procedure. The median hospital length of stay was calculated for each diagnostic group, and compared between cohorts using the Wilcoxon rank sum test. Crude incidence rates (*IR*) of hospital admissions were calculated for each birth-cohort, diagnostic group and age group, and incidence rate ratios (*IRR*) were calculated between the VNEC and VEC assuming Poisson variance. The proportion of hospitalizations which led to admission to the intensive care unit (ICU) was calculated by birth-cohort and diagnostic group.

The Kaplan-Meier product limit estimator was used to calculate both event-free survival, as well as the event-free survival difference of the VNEC compared to the VEC for each of the diagnostic groups. Subsequent hospitalizations of the same child with the same discharge diagnosis were excluded from this portion of the analysis. Follow-up time was censored upon emigration or death. Cox regression was used to estimate the hazard ratio of admission between the VNEC and VEC. To clarify whether potential differences between VNEC and VEC were likely to be due to direct effects of the vaccine, the Cox regression was repeated for two restricted age-ranges; 0-90 days of age and 90 days and older. A sensitivity analysis of potential unmeasured confounding of the hazard ratio was calculated using E-values (VanderWeele and Ding 2017). An E-value represents the minimum association which an unmeasured confounder would need to have with both the exposure and the outcome, to completely explain away the observed association.

### **3.7 Impact and cost-effectiveness analysis (Paper VI)**

The objective of Paper VI was to estimate the population impact of PHiD-CV10 on several aspects of pneumococcal disease, and to calculate the cost-effectiveness of PHiD-CV10 introduction. Considered were otitis media visits to primary care among children zero to 19 years of age, and hospitalizations due to pneumonia and invasive pneumococcal disease among the whole population. The study period was from 1 January 2005 to 31 December 2017 and the study population included all Icelandic citizens. The data were analyzed as a time series, and incorporated synthetic controls.

### **3.7.1 Data sources**

Data were extracted from several population-based registries. Primary care visits with ICD-10 diagnoses compatible with otitis media (H65, H66, H70, H72) were extracted from the Primary Care Registry. The observation period was restricted to 2005-2015, as the Primary Care Registry was not updated for 2016 and 2017. Data regarding hospitalized pneumonia and invasive pneumococcal disease were extracted from Landspítali University Hospital's patient registry. Microbiological data were extracted from a database maintained by the Department of Clinical Microbiology at Landspítali University Hospital and linked to the patient registry. A hospitalization was considered to be due to invasive pneumococcal disease if associated with culture or PCR-confirmed *Streptococcus pneumoniae* sampled from joint fluid, bone, cerebrospinal fluid or blood, regardless of ICD-10 discharge diagnosis. Hospitalizations with ICD-10 diagnoses compatible with pneumonia (J12-J18) were obtained directly from the patient registry. The aggregate number of visits and hospitalizations per calendar-month for diagnoses unrelated to *Streptococcus pneumoniae* infections were also extracted from both registries and used as synthetic controls (Table 10).

The direct costs of hospitalization were obtained from the patient registry. For each hospitalization or emergency department visit, a detailed breakdown of cost was available, which was extracted for each of the disease categories included in the study. No cost data was available for primary care visits. Because Children's Hospital Iceland's pediatric emergency department serves as a walk-in clinic for the greater capital area, the distribution of costs for otitis media visits to the emergency department was assumed to mirror that of primary care visits, and was used in its stead. The number of PHiD-CV10 doses purchased by the government and the unit price for each dose per calendar year were obtained directly from the Icelandic Directorate of Health. The yearly employment rate of individuals 15 to 24 years of age, 25 to 54 years of age and 55 to 64 years of age from 2011-2017 was extracted from Organization for Economic Cooperation and Development (OECD) Labour Force Statistics (*OECD Labour Force Statistics* 2018), and the deciles of regular total wage for working Icelanders from 2011-2017 were obtained from Statistics Iceland. The consumer price index for medical care obtained from Statistics Iceland was used to convert all direct health care costs to 2015 price levels in Icelandic kronas. All costs were converted to United States Dollars (USD) using the official exchange rates of the Icelandic Central Bank.

### **3.7.2 Impact of PHiD-CV10**

The impact of PHiD-CV10 introduction on the incidence of pneumococcal disease was estimated and the results then used as an input for a cost-effectiveness analysis. This was accomplished using a previously published Bayesian time series methodology (Bruhn et al. 2017; Shioda et al. 2018). The pre-vaccine period was defined as 1 January 2005 to 31 December 2010, and the post-vaccine period as 1 January 2013 to 31 December 2017. A transition period was included from 2011 to 2012. For each disease category and age-group, four models of PHiD-CV10 impact were estimated. All were Bayesian Poisson models with observation specific random intercepts to account for over-dispersion (???). Each model utilized the pre-vaccine period to predict the monthly occurrence of the outcome of interest in the post-vaccine period, had the vaccination not occurred.

The simplest model was an interrupted time series (ITS) model without an offset term. Calendar-month effects were accounted for using dummy variables. The ITS model used the pre-vaccine period to estimate the trend. It predicted the monthly number of cases of the disease category, assuming the pre-vaccine trend would have continued if the vaccination had not occurred. A second ITS model was estimated, which included an offset term of all non-respiratory visits. This model used the pre-vaccine period to estimate the relationship between the outcome of interest and all non-respiratory visits. It also predicted the occurrence of disease in the post-vaccine period by incorporating the observed number of non-respiratory visits, and assumed the relationship between the disease category and non-respiratory visits would not have changed, had the vaccination not occurred. The third model included synthetic controls as covariates and used Bayesian variable selection to choose which of them to include (Bruhn et al. 2017). The prior for each synthetic control was set as a Dirac spike with a point-mass at zero. The pre-vaccine period was used to estimate the relationship between the synthetic controls and the outcome of interest, and to select the optimal controls. This relationship was used to predict the trend in the post-vaccine period, had the vaccination not occurred. Finally, a two-step model was fitted, using a seasonal and trend decomposition (STL) and principal component analysis (PCA) (Shioda et al. 2018). STL was used to extract a smoothed trend for each of the synthetic controls. PCA was then used to extract the first principal component, which was used as a covariate in the final prediction model.

Using data from the pre-vaccine period, leave-one-out cross-validation (LOOCV) was used to calibrate the models and calculate the average point-wise likelihood for each model, diagnostic category and age-group. The average point-wise likelihoods were used as weights in a Bayesian model-stacking procedure, to produce the final stacked model used in the analysis. From the posterior predictive distribution of the stacked model, a total of 10,000 Markov chain Monte Carlo (MCMC) samples were drawn, representing the number of cases that would have occurred in the post-vaccine period, had the vaccine not been introduced. The first 2,000 MCMC draws were discarded for optimal burn-in. For each of the remaining 8,000 draws, the rate ratio between the observed and predicted number of cases during the post-vaccine period was calculated, and the median and 95% credible intervals extracted from the resulting distribution of rate ratios. To estimate the onset of vaccine impact, the rate ratio was calculated over a rolling 12-month period, the first of which included 11-months of pre-vaccine data and one month of post-vaccine data. The number of cases prevented by the vaccine was calculated for each calendar-month, by subtracting the observed number of cases from each of the 8,000 MCMC draws. The cumulative sum of prevented cases was calculated, and the median and 95% credible intervals were extracted.

### 3.7.3 Cost-effectiveness analysis

The cost-effectiveness of PHiD-CV10 introduction compared to no intervention was estimated from both the healthcare sector and societal perspectives using ecological post-implementation data. The societal perspective included both direct costs and indirect costs associated with productivity loss, while analysis from the health care perspective included only direct costs. Neither analysis included estimates of long-term sequelae or their associated costs. The time horizon was five years and both costs and cost-savings were discounted at a 3% discount rate. All costs were presented in constant 2015 USD.

The direct cumulative savings associated with PHiD-CV10 introduction were calculated by multiplying the predicted number of prevented cases from the Bayesian time series analysis with the expected cost of each case. The expected cost was obtained through sampling with replacement from the observed costs extracted from Landspítali University Hospital's patient registry, after adjusting to constant 2015 Icelandic kronas and converting to USD. The sampling was stratified by disease category and age-group. The direct costs associated with the introduction of PHiD-CV10 into the pediatric

vaccination program were calculated for each calendar-year by multiplying the number of purchased doses by the price of each purchased dose. The prices were adjusted to constant 2015 Icelandic kronas and converted to USD. Wastage was taken into account, as this formula included doses that were for whatever reason never administered. Additional administration costs were however not assumed, as each dose was administered by nurses during the same visits that other established vaccines were being given. The direct costs associated with the vaccine were subtracted from the direct cumulative savings to obtain the final estimate of the total cost. This resulted in 8,000 posterior draws of the total cost, from which the median and 95% credible intervals were extracted.

Indirect costs due to productivity loss were accounted for in the analysis from the societal perspective. The deciles of wage that were extracted from Statistics Iceland were optimally fitted to a lognormal distribution to obtain a continuous distribution of wage (???). The number of days of work lost were assumed. For each case of otitis media in primary care, the days of work lost by a parent or guardian were assumed to follow a Poisson distribution with mean equaling one. For each pneumonia or invasive pneumococcal disease hospitalization, the days of work lost were assumed to equal the sum of the hospital length of stay and a variable time following discharge. For each prevented case, the associated hospital length of stay was sampled with replacement from the observed length of stay obtained from the patient registry. This variable time was assumed to be Poisson distributed with mean equal to half the observed hospital length of stay. The indirect costs were calculated by multiplying the days of work lost with wages sampled from the lognormal wage distribution, accounting for unemployment. Cost-effectiveness was summarized with incremental cost-effectiveness ratios (ICER) with 95% credible intervals.



## 4 Results

### 4.1 Data collection and sources

The data presented in this thesis span a period from 2005-2017 and were collected and analyzed over a four year period from 2013-2017. Consequently, the papers that form this thesis were written and published at different times. For this reason, the study period and the populations described in each paper varies slightly. However, they differ only marginally from the final data summary described below. The results of papers I-VI are summarized in their respective sub-chapters.

When data from all registries were taken together, individual-level information was available for 375,383 Icelandic citizens, of which 183,544 were female and 181,316 were male. Gender was not registered for 10,523 individuals. The exact date of birth was available for 366,188, and birth-year for the rest. The median birth-year for the whole study population was 1979 (IQR 1958-1997). Death was registered for 12,308 individuals.

The study often examined data stratified by birth-cohort. The number of children in each birth-cohort who contributed data to the present study is shown in Table 14.

Table 14. Demographic information regarding birth-cohorts included in the study. The number of children and proportion who are male is presented. The number of children in each cohort who had registered immigration or emigration from Iceland before four years of age is shown.

Birth-cohort	No. children	Proportion male (%)	No. moved
2005	4,803	51.5	578
2006	4,887	51.4	572
2007	4,993	51.6	567
2008	5,153	51.7	571
2009	5,331	51.7	553
2010	5,203	51.4	525
2011	4,849	51.7	473
2012	4,841	51.2	430
2013	4,566	49.4	344

2014	4,527	51.1	223
2015	4,198	51.3	144
2016	4,112	50.7	26

#### 4.1.1 Statistics Iceland

Statistics Iceland ([www.statice.is](http://www.statice.is)) provided data on the immigration and emigration of all Icelandic children zero to four years of age from 2005-2017. Of the 57,695 Icelandic children born 2005 or later, 5,577 moved to or from the country 6,847 times. The proportion of children in each birth-cohort who moved at least once before five years of age, was consistently 9%-12% of those birth-cohorts who had full five year follow-up time with regards to immigration and emigration (birth-cohorts 2005-2012).

#### 4.1.2 Landspítal University Hospital patient registry

All visits and hospitalizations with ICD-10 diagnostic codes compatible with respiratory infections (Table 8), and procedural codes compatible with tympanostomy tube procedures (Table 9), were extracted from Landspítal's patient registry. The number of visits and hospitalizations of all age-groups corresponding to each of the study's ICD-10 codes recorded as the primary diagnosis, are shown in Table 15.

Table 15. The number of visits and hospitalizations with International Classification of Diseases, 10th revision (ICD-10) codes listed as the primary diagnosis. Hospital visits and hospitalizations are extracted from Landspítal University Hospital's patient registry between 1 January 2005 and 31 December 2017. Primary care visits are obtained from the Primary Care Registry of the Icelandic Directorate of Health from 1 January 2005 to 31 December 2015.

ICD-10 code	Disease	Hospital visits	Hospital admissions	Primary care visits
A40	Streptococcal sepsis	37	135	68
A41	Other sepsis	370	777	279
A48	Other bacterial diseases, not elsewhere classified	5	28	10
A49	Bacterial infection of unspecified site	123	26	1,861
B00	Herpesviral [herpes simplex] infections	497	22	2,176

B08	Other viral infections characterized by skin and mucous membrane lesions, not elsewhere classified	76	1	655
B33	Other viral diseases, not elsewhere classified	32	4	106
B34	Viral infection of unspecified site	25,601	528	329,179
B95	Streptococcus, Staphylococcus, and Enterococcus as the cause of diseases classified elsewhere	12	4	40
B96	Other bacterial agents as the cause of diseases classified elsewhere	5	7	29
G00	Bacterial meningitis, not elsewhere classified	79	60	3
H65	Nonsuppurative otitis media	2,803	75	38,585
H66	Suppurative and unspecified otitis media	11,647	244	160,086
H70	Mastoiditis and related conditions	164	86	259
H72	Perforation of tympanic membrane	1,270	233	1,947
H73	Other disorders of tympanic membrane	67	3	727
J00	Acute nasopharyngitis [common cold]	3,525	49	124,984
J01	Acute sinusitis	4,625	113	152,076
J02	Acute pharyngitis	1,869	44	124,874
J03	Acute tonsillitis	5,019	213	106,491
J04	Acute laryngitis and tracheitis	983	38	19,288
J05	Acute obstructive laryngitis [croup] and epiglottitis	2,738	40	3,148

J06	Acute upper respiratory infections of multiple and unspecified sites	3,649	94	110,236
J09	Influenza due to certain identified influenza viruses	250	185	9
J10	Influenza due to other identified influenza virus	282	151	699
J11	Influenza due to unidentified influenza virus	1,003	77	34,949
J12	Viral pneumonia, not elsewhere classified	206	189	189
J13	Pneumonia due to Streptococcus pneumoniae	129	265	80
J14	Pneumonia due to Hemophilus influenzae	18	44	34
J15	Bacterial pneumonia, not elsewhere classified	2,489	1,129	1,870
J16	Pneumonia due to other infectious organisms, not elsewhere classified	60	37	62
J17	Pneumonia in diseases classified elsewhere	17	15	38
J18	Pneumonia, unspecified organism	8,576	4,501	66,232
J20	Acute bronchitis	2,431	297	148,963
J21	Acute bronchiolitis	2,874	707	6,178
J22	Unspecified acute lower respiratory infection	356	55	9,425
J32	Chronic sinusitis	3,298	405	52,899
J36	Peritonsillar abscess	1,095	254	1,239
J40	Bronchitis, not specified as acute or chronic	893	49	77,272
J85	Abscess of lung and mediastinum	98	41	24
J86	Pyothorax	20	62	48

J90	Pleural effusion, not elsewhere classified	560	409	599
N30	Cystitis	6,112	568	133,560
N39	Other disorders of urinary system	12,901	2,868	36,154
R05	Cough	2,471	11	83,948
R50	Fever of other and unknown origin	3,433	557	27,121

In total, 169,585 contacts (of 74,740 individuals) with the study's ICD-10 codes were recorded, of which 135,841 (64,090) were visits to outpatient clinics or emergency departments and 33,744 (20,318) were hospital admissions. The highest recorded number of visits of a single individual was 170 and the most admissions was 31. The number of procedures performed at Landspítali University Hospital is shown in Table 16.

Table 16. The number of NOMESCO Classification of Surgical Procedures (NCSP) performed at Landspítali University Hospital between 1 January 2005 and 31 December 2017. The data is presented for all age-groups.

NCSP code	Description	Number of procedures
EMSB00	Excision of lesion of tonsil or adenoid	1
EMSB10	Tonsillectomy	88
EMSB15	Intracapsular destruction of tonsils	2
EMSB20	Adenotonsillectomy	101
EMSB30	Adenectomy	170
EMSB99	Other excision on tonsils and adenoids	2
EMSW99	Other operation on tonsil or adenoids	1
DCSA10	Paracentesis of tympanic membrane	289
DCSA20	Insertion of ventilating tube through tympanic membrane	340
DCSW00	Removal of ventilating tube from tympanic membrane	0

The age distribution of visits and hospital admissions is shown in Figure 1. Though children and young adults comprised most of the visits due to study diagnoses, older adults made up the largest number of hospitalizations.

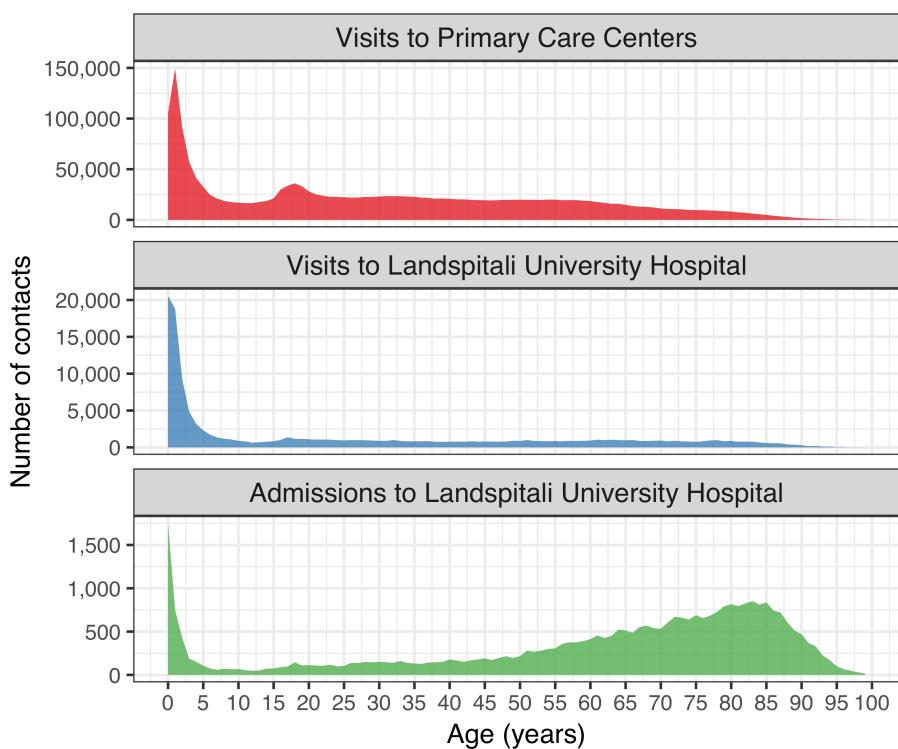


Figure 1. The total number of contacts to Landspítali University Hospital and Primary Care Centers in Iceland associated with International Classification of Diseases, 10th revision (ICD-10) codes compatible with respiratory infections. Data on hospital contacts were extracted from Landspítali University Hospital's patient registry from 1 January 2005 to 31 December 2017. Primary care contacts were obtained from the Primary Care Registry of the Icelandic Directorate of Health from 1 January 2005 to 31 December 2015. The number of contacts is shown as a function of age. Different Y-axis scales are used for each category. The figure demonstrates disproportionate hospitalizations among older adults, compared to primary care contacts and hospital visits.

In addition to the increased frequency of hospitalization among older adults, the cost associated with each visit and hospitalization was higher (Figure 2).

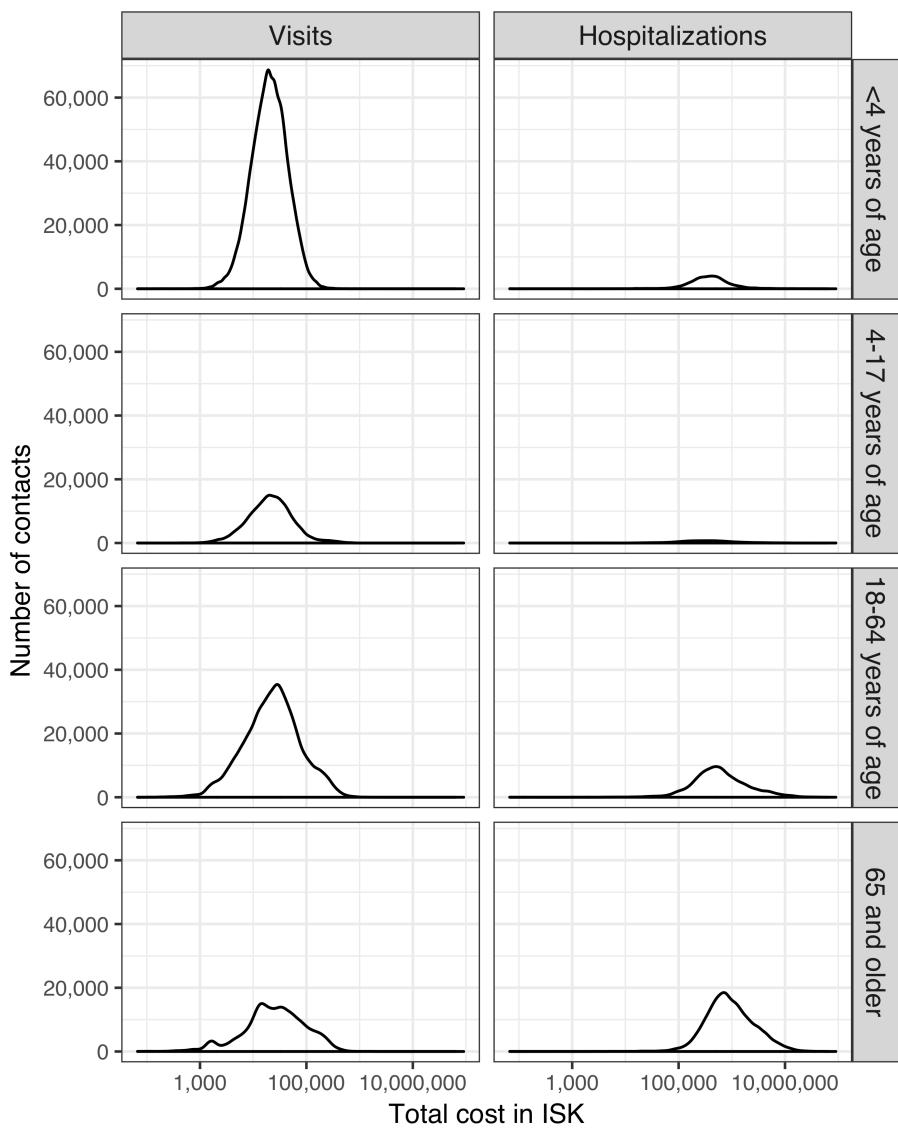


Figure 2. The distribution in the cost associated with contacts to Landspítali University Hospital was extracted from the patient registry for the period of 1 January 2005 to 31 December 2017. Costs are presented in Icelandic Krona (ISK) at the value of the calendar year in which they occurred. Distributions are presented separately for visits and hospitalizations, and are further divided into age-groups. The X-axis has been logarithmically scaled. The figure shows that costs associated with visits range from 1,000 ISK to 100,000 ISK, while hospitalizations range from 100,000 ISK to 10,000,000 ISK. As age increases, the distribution shifts towards higher costs.

#### 4.1.3 The Primary Care Registry

The Primary Care Registry contains information on all primary care health contacts for the period 2005-2015. All contacts associated with the ICD-10 codes listed in Table 8, regardless of age, were extracted. A total of 1,963,439 separate contacts were recorded between 298,307 individual patients and 1,266 different physicians. The most visits recorded for a single individual was 212. The distribution of contacts by age can be seen in Figure 1.

#### 4.1.4 The National Vaccine Registry

The National Vaccine Registry contains information on all administered vaccine doses for the period 2005-2017. All recorded pneumococcal vaccine doses were extracted using ATC code J07 and sub-levels. A total of 110,712 doses of pneumococcal vaccines were administered to 51,601 individuals during the study period. The monthly number of administered doses per age-group and vaccine is shown in Figure 3.

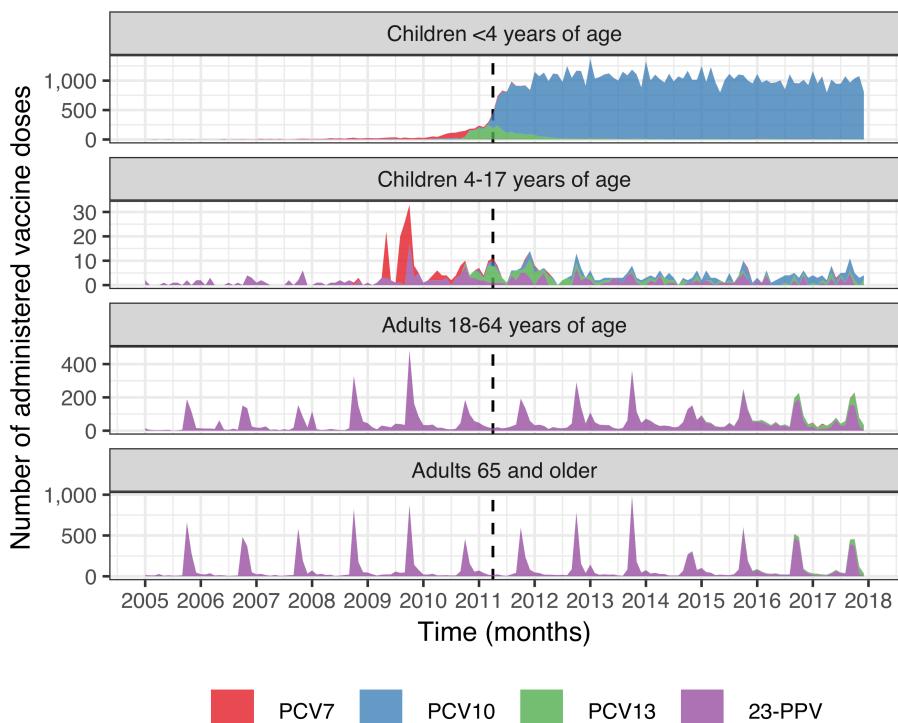


Figure 3. The monthly number of administered doses of pneumococcal vaccines in Iceland from 1 January 2005 to 31 December 2017. Data were extracted from the National Vaccine Registry of the Icelandic Directorate of Health using Anatomical

Therapeutic Chemical code J07. Records were available for four different pneumococcal vaccines; the 23-valent pneumococcal polysaccharide vaccine (23-PPV, purple), seven-valent pneumococcal conjugate vaccine (PCV7, red), the 10-valent pneumococcal conjugate vaccine (PCV10, blue) and the 13-valent pneumococcal conjugate vaccine (PCV13, green). The introduction of PCV10 into the Icelandic pediatric vaccination program on 1 April 2011, is shown with a dotted line. Different Y-axis scales are used for each category of age. The figure demonstrates the abrupt and sustained increase in the number of administered doses of PCV10 following introduction into the vaccine program. Adult vaccination with 23-PPV does not appear to have increased during the study period.

Table 17 shows the number of children in each birth-cohort who had received zero, one, two, or three doses of a pneumococcal conjugate vaccine by four years of age. An abrupt shift is observed in the first vaccine eligible cohort, of which over 90% received three or more doses of a pneumococcal conjugate vaccine. Children who moved to or from the country before four years of age, were excluded from the table.

Table 17. The number of children in each birth-cohort who received zero to three doses of a pneumococcal conjugate vaccine before four years of age. The percentage of children receiving each number of doses is given within parentheses. Children who were documented to have immigrated or emigrated from Iceland before four years of age were excluded. For the remaining children, data were obtained from the National Vaccine Registry of the Icelandic Directorate of Health using Anatomical Therapeutic Chemical code J07 for the period from 1 January 2005 to 31 December 2017. Seven-, 10- and 13- valent pneumococcal conjugate vaccines were included. At the end of the observational period, some children in the 2016 birth-cohort had not yet reached the age during which it is common to receive the third vaccine dose.

Birth-cohort	Zero doses	One dose	Two doses	Three doses
2005	4,207 (99.6)	10 (0.2)	5 (0.1)	4 (0.1)
2006	4,278 (99.1)	26 (0.6)	8 (0.2)	3 (0.1)
2007	4,345 (98.1)	51 (1.2)	18 (0.4)	13 (0.3)
2008	4,348 (94.8)	140 (3.1)	62 (1.4)	37 (0.8)
2009	4,292 (89.8)	166 (3.5)	237 (5.0)	87 (1.8)
2010	3,660 (77.8)	158 (3.4)	336 (7.1)	549 (11.7)
2011	263 (5.9)	44 (1.0)	144 (3.3)	3,976 (89.8)
2012	199 (4.5)	45 (1.0)	154 (3.5)	4,059 (91.1)
2013	165 (3.9)	44 (1.0)	122 (2.9)	3,940 (92.3)
2014	127 (2.9)	54 (1.2)	191 (4.4)	3,978 (91.4)
2015	70 (1.7)	60 (1.5)	283 (6.9)	3,672 (89.9)
2016	45 (1.1)	76 (1.9)	466 (11.4)	3,514 (85.7)

Some children in vaccine non-eligible cohorts received one, two or three doses of pneumococcal conjugate vaccines before four years of age. This generally occurred at an older age than children in the vaccine eligible cohorts Figure 4.

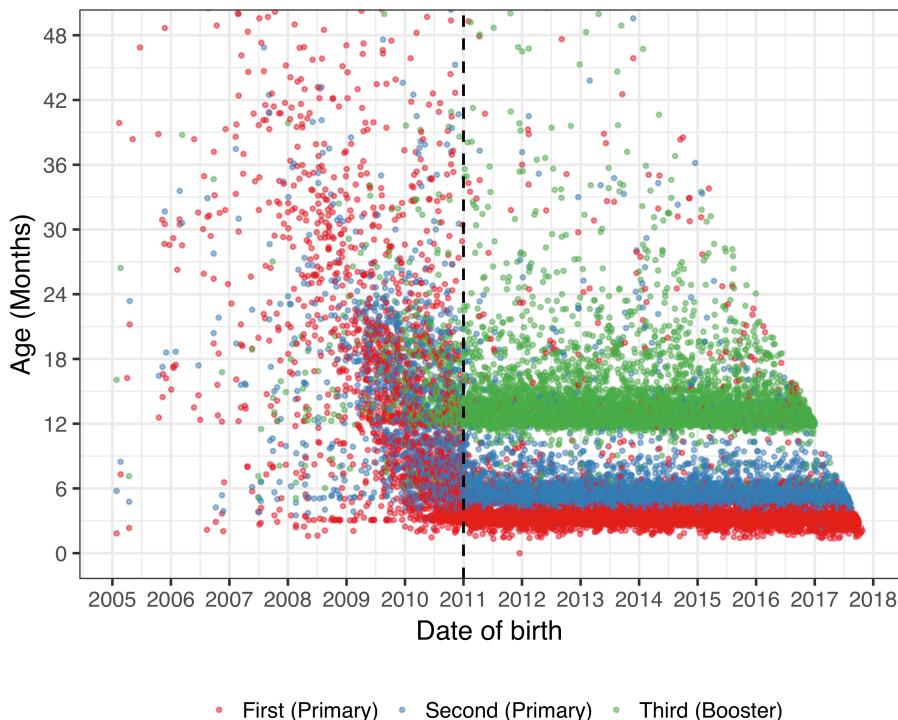


Figure 4. The age at which children receive their first, second and third dose of a pneumococcal conjugate vaccine (PCV) as a function of birth-date. All administered doses of PCV were extracted from the National Vaccine Registry of the Icelandic Directorate of Health from 1 January 2005 to 31 December 2017, using Anatomical Therapeutic Chemical code J07. The age at which each individual child received a dose of PCV is illustrated with a point. The child's first documented dose is indicated in red color, their second dose in blue and their third dose in green. The introduction of PCV10 into the Icelandic pediatric vaccination program on 1 April 2011, is shown with a dotted line. Though some children received PCV prior to the vaccine introduction, they did so sporadically, and few achieved two or more doses. Those who did were almost invariably born in the latter half of 2010. An obvious change occurs after vaccine introduction. The apparent oblique cut-off in points starting for children born in 2014 is explained by censored follow-up time.

The National Drug Prescription Registry (NDPR) contains all filled outpatient prescriptions from 2005-2017. From this registry, all antibacterials for systemic use (ATC code J01 and sub-levels), vaccines (J07 and sub-levels), ophthalmologicals (S01 and sub-levels) and otologicals (S02 and sub-levels)

were extracted. A total of 4,020,624 prescriptions were recorded among 360,560 individuals. The number of prescriptions by the chemical sub-levels of the ATC classification system are shown in Table 18. The highest number of antimicrobial prescriptions filled by a single individual was 336 during the study period.

Table 18. The number of filled outpatient prescriptions by Anatomical Therapeutic Chemical (ATC) is shown for the period from 1 January 2005 to 31 December 2017. Data were extracted from the National Drug Prescription Registry of the Icelandic Directorate of Health.

ATC chemical sub-level code	Description	No of prescriptions
J01A	Tetracyclines	357,498
J01B	Amphenicols	0
J01C	Beta-lactam antibacterials, penicillins	1,720,661
J01D	Other beta-lactam antibacterials	106,757
J01E	Sulfonamides and trimethoprim	168,045
J01F	Macrolides, lincosamides and streptogramins	344,098
J01G	Aminoglycoside antibacterials	71
J01M	Quinolone antibacterials	135,864
J01R	Combinations of antibacterials	0
J01X	Other antibacterials	96,318
J07A	Bacterial vaccines	9,687
J07B	Viral vaccines	16,703
J07C	Bacterial and viral vaccines	496
J07X	Other vaccines	0
S01A	Anti-infective ophthalmologicals	287,904
S02A	Anti-infective otologicals	1
S01C	Anti-inflammatory agents and anti-infectives ophthalmologicals	40,315
S02C	Anti-inflammatory agents and anti-infectives otologicals	25,218

The distribution in the number of prescriptions for selected chemical sub-levels of the ATC classification system are shown as a function of age in Figure 5.

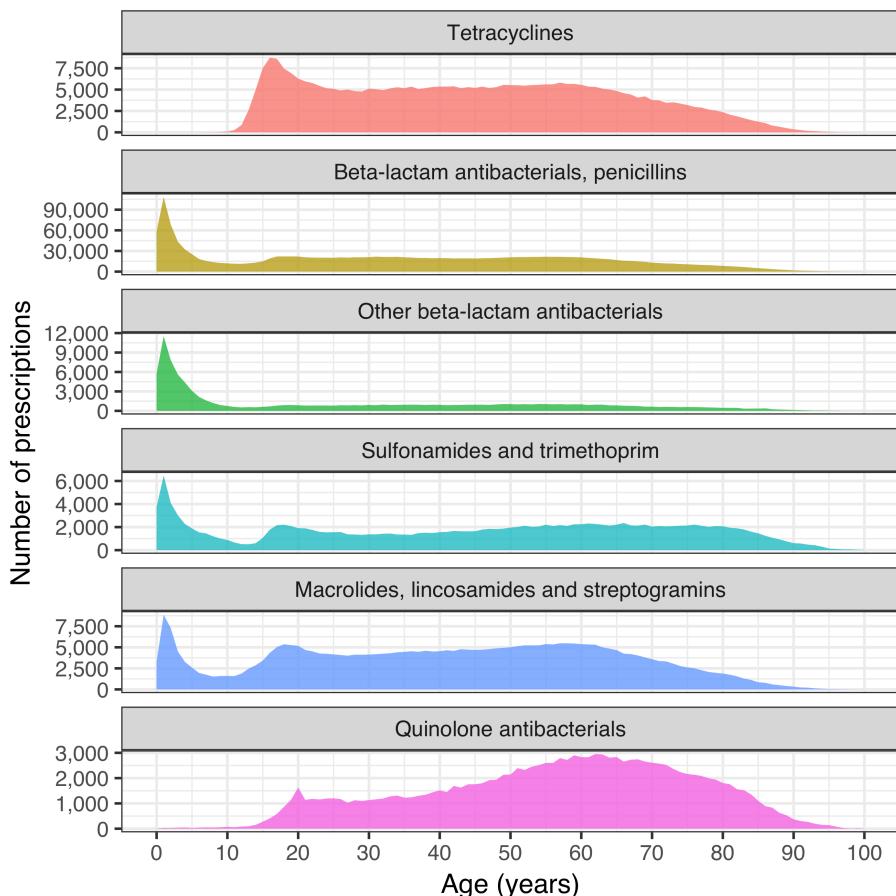


Figure 5. The number of filled antimicrobial prescriptions as a function of age for selected chemical sub-levels of the Anatomical Therapeutic Chemical (ATC) classification system. Data were extracted from the National Drug Prescription Registry of the Icelandic Directorate of Health for the period of 1 January 2005 to 31 December 2017. Different Y-axis scales are used for each category. The figure demonstrates a similar age-distribution for beta-lactam antibacterials, sulfonamides and macrolides, with most prescriptions being filled by young children. Tetracyclines and quinolones are more commonly filled by adults.

#### 4.1.5 Reimbursement database of Icelandic Health Insurance

All interactions with independent health care practitioners were recorded in Icelandic Health Insurance's reimbursement database. From this database, all records of otolaryngological procedures were extracted. A total of 51,814

procedures were recorded among 34,084 individuals (Table 19). In total, 16,096 tonsillectomies and 29,689 tympanostomy tube placements were performed. The absolute number of adenoidectomies performed in Iceland cannot be deduced from the reimbursement database as the reimbursement codes for tonsillectomies are the same whether or not an adenoidectomy was performed concurrently.

Table 19. The number of procedures reimbursed to independently practicing otolaryngologists from 1 January 2005 to 31 December 2016. Data were extracted from the reimbursement database of Icelandic Health Insurance. Tympanostomy tube placements for which an anesthesiologist also received reimbursement were performed under general anesthesia. Others were categorized as TTP without mention of anesthetic. The total number of adenoidectomies performed in Iceland cannot be deduced from the reimbursement data, because the same reimbursement code is used for tonsillectomies with or without adenoidectomies. However, a separate reimbursement code always exists for procedures including TTP.

Procedure	No of procedures
Adenoidectomy	2,442
Adenoidectomy and TTP	10,849
Myringoplasty	135
Myringotomy under local anesthetic	1,004
Tonsillectomy (+/- adenoidectomy)	9,383
Tonsillectomy (+/- adenoidectomy) and TTP	31
Tonsillectomy performed with laser (+/- adenoidectomy)	4,996
Tonsillectomy performed with laser (+/- adenoidectomy) and TTP	686
TTP under general anesthesia	16,829
TTP without mention of anesthetic	294
Tympanostomy tube removal	5,165

## 4.2 Impact on otitis media with treatment failure (Paper I)

The total number of children under 18 years of age who lived within Children's Hospital Iceland's referral region remained stable during the study period from 1 January 2008 to 31 December 2015, decreasing from 62,067 in to 61,798. The variation in the number of children under four years of age in the same region was more pronounced, increasing from 13,562 in 2008 to 14,644 in 2011, and then decreasing again to 13,272 in 2015.

During the study period, 103,220 visits were recorded to the emergency department of Children's Hospital Iceland. The visits varied over the calendar year, spiking in the winter months and troughing in the summer months. The total number of visits increased steadily during the study period, from 12,229 in 2008 to 14,502 in 2015 (Figure 6).

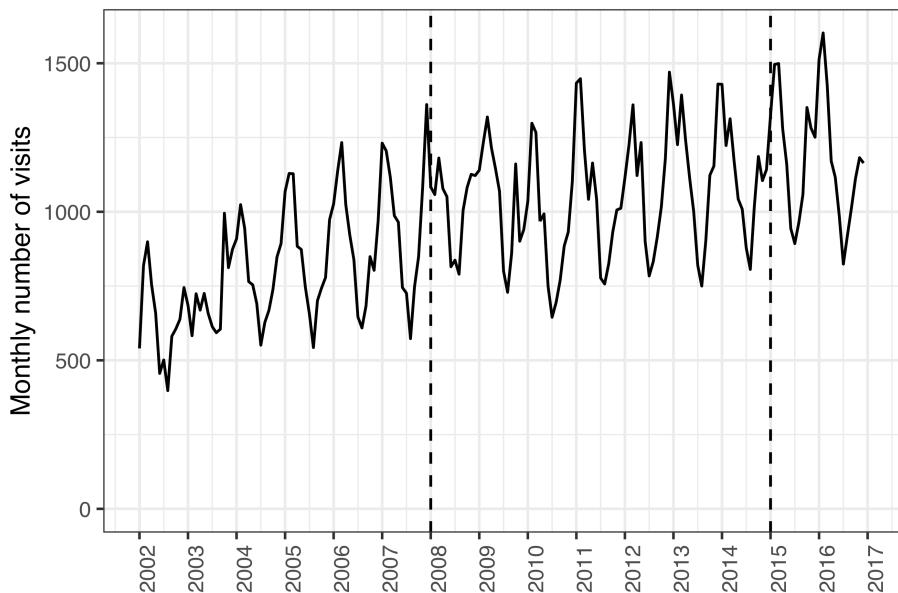


Figure 6. The monthly number of visits of children zero to 18 years of age to Children's Hospital Iceland's emergency department during the period from January 2002 to December 2016. All visits are included regardless of International Classification of Diseases, 10th revision (ICD-10) diagnostic codes. The study period was from January 2008 to December 2015, and is delineated with two vertical dashed lines.

During the same period, 6,232 visits to the Children's Hospital Iceland for acute otitis media were recorded for 4,624 individual children under four years of age, representing 4,994 distinct episodes. Of those episodes, 531 were treated with one or more doses of ceftriaxone. The total number of visits, visits for AOM and ceftriaxone treatment episodes are shown in Table 20.

Table 20. The incidence of visits and ceftriaxone treatment episodes at Children's Hospital Iceland by calendar-year. The incidence is both presented for all visits regardless of diagnosis (Total) and visits associated with acute otitis media (AOM). When presented for total visits or treatment episodes regardless of diagnosis, the denominator is children 18 and younger who live within Children's Hospital Iceland's referral region and is expressed per 1,000 visits or person-years. The denominator of AOM associated visits or treatment episodes are children younger than four years of

age in the same region. The incidence rate and incidence risk are shown with the number of events within parentheses

			Incidence rate of parenteral ceftriaxone			
Incidence rate of visits			Per 1,000 visits		Per 1,000 person-years	
Year	Total (n)	AOM (n)	Total (n)	AOM (n)	Total (n)	AOM (n)
2008	197 (12,229)	69 (936)	80.8 (988)	186 (174)	15.9 (988)	72.9 (174)
2009	199 (12,514)	72 (1,012)	74.8 (936)	192 (194)	14.9 (936)	66.5 (194)
2010	181 (11,339)	64.2 (925)	81 (918)	253 (234)	14.6 (918)	63.7 (234)
2011	201 (12,645)	60.8 (890)	63.8 (807)	178 (158)	12.8 (807)	55.1 (158)
2012	215 (13,150)	58.4 (830)	52.5 (691)	163 (135)	11.3 (691)	48.6 (135)
2013	221 (13,518)	55.2 (772)	54.7 (739)	105 (81)	12.1 (739)	52.8 (81)
2014	216 (13,323)	52 (708)	48.9 (652)	76.3 (54)	10.6 (652)	47.9 (54)
2015	235 (14,502)	55.1 (731)	56.7 (822)	88.9 (65)	13.3 (822)	61.9 (65)

The incidence rate of AOM visits to Children's Hospital Iceland decreased significantly in the post-vaccine period as compared to the pre-vaccine period; from 47.4 visits to 41.8 per 1,000 person-years. The crude IRR was 0.88 (95% CI 0.83 to 0.93). Mantel-Haenszel adjustment was not appropriate due to effect heterogeneity ( $\chi^2 = 15.2$ ,  $P<0.001$ ). When each age-group was examined separately, a significant decrease in AOM visits was observed among children between one and two years of age (IRR 0.89) and between two and three years of age (IRR 0.79) as shown in Table 21. Children younger than one year of age and children between three and four years of age, visited the Children's Hospital Iceland because of AOM 471 times and 379 times, respectively.

Table 21. The incidence rate ratios (IRR) of acute otitis media (AOM) associated visits between the pre- and post-vaccine periods by age. The 95% confidence intervals are presented within parentheses. The chi-squared statistic and P-value are also presented.

Age (years)	IRR (95% CI)	Chi-squared	P-value
<1	1.10 (0.90-1.30)	0.80	0.370
1-2	0.89 (0.83-0.96)	8.60	0.003
2-3	0.79 (0.71-0.88)	17.0	< 0.001
3-4	1.00 (0.85-1.30)	0.22	0.639

Independent of the decrease in AOM associated visits to the Children's Hospital, the incidence of ceftriaxone treatment episodes for AOM was also found to decrease significantly in the post-vaccine period compared to the pre-vaccine period. The effect was heterogeneous across age-strata ( $\chi^2 = 57$ ,  $P<0.001$ ) and the crude overall IRR was 0.48 (95% CI 0.40 to 0.58). The stratum specific results are shown in Table 22. During the study period, only 17 episodes of AOM were treated with ceftriaxone among children zero to one years of age and 19 episodes were treated among children three to four years of age.

Table 22. The incidence rate ratios (IRR) of ceftriaxone treatment episodes of otitis media (AOM) between the pre- and post-vaccine periods by age. The 95% confidence intervals are presented within parentheses. The chi-squared statistic and P-value are also presented.

Age (years)	IRR (95% CI)	Chi-squared	P-value
<1	0.61 (0.19-1.80)	0.96	0.326
1-2	0.47 (0.37-0.60)	41.0	<0.001
2-3	0.47 (0.32-0.68)	18.0	<0.001
3-4	0.85 (0.31-2.30)	0.12	0.732

The risk of receiving ceftriaxone treatment if presenting to Children's Hospital Iceland with AOM was calculated in order to correct for the possibility that observed decreases in ceftriaxone treatment episodes were due only to a decrease in the number of AOM associated visits. The risk decrease was not homogeneous across age-strata ( $\chi^2 = 33.8$ ,  $P<0.001$ ) and the overall relative risk ratio was 0.58 (95% CI 0.48 to 0.69). The stratum specific effects are shown in Table 23.

Table 23. The incidence risk ratio (IRR) of receiving ceftriaxone treatment if presenting to Children's Hospital Iceland with acute otitis media (AOM) between the

pre- and post-vaccine periods by age. The 95% confidence intervals are presented along with the corresponding Chi-squared statistic and P-value.

Age (years)	IRR (95% CI)	Chi-squared	P-value
<1	0.56 (0.17-1.70)	1.30	0.258
1-2	0.53 (0.42-0.67)	26.0	< 0.001
2-3	0.59 (0.40-0.86)	7.50	0.006
3-4	0.81 (0.29-2.20)	0.19	0.662

Thus, the study found significant decreases in the incidence of AOM visits, ceftriaxone treatment episodes of AOM and risk of ceftriaxone treatment if presenting to the Children's Hospital Iceland with AOM. Similar decreases were established in the ceftriaxone treatment episodes for pneumonia. In the pre-vaccine period, 251 treatment episodes were recorded, compared to only 90 in the post-vaccine period. The effect was not consistent across age-strata ( $\chi^2 = 72$ ,  $P<0.001$ ). The overall IRR was 0.37 (95% CI 0.29 to 0.47). The stratum specific effects are shown in Table 24.

Table 24. The incidence rate ratio (IRR) of ceftriaxone treatment episodes of pneumonia between the pre- and post-vaccine periods are presented along with 95% confidence intervals. The chi-squared statistic and P-values are also shown.

Age (years)	IRR (95% CI)	Chi-squared	P-value
<1	0.15 (0.017-0.64)	8.6	0.003
1-2	0.34 (0.220-0.51)	33.0	< 0.001
2-3	0.36 (0.230-0.54)	28.0	< 0.001
3-4	0.51 (0.290-0.89)	6.4	0.012

To ascertain whether a decrease in ceftriaxone use occurred in vaccinated children for non-vaccine related indications, the incidence of ceftriaxone treatment episodes for all other indications was examined. No heterogeneity across age-strata was detected ( $\chi^2 = 0.56$ ,  $P=0.455$ ). The Mantel-Haenszel adjusted IRR was 0.96 (95% CI 0.87 to 1.06), and the null hypothesis of no difference in the incidence rate of treatment episodes could not be rejected. The number of treatment episodes by age and vaccine period ranged from 117 to 295. The stratum specific IRR are shown in Table 25.

Table 25. The incidence rate ratios (IRR) of ceftriaxone treatment episodes for indications other than acute otitis media and pneumonia between the pre- and post-vaccine periods for each age. The 95% confidence intervals are presented within parentheses. The chi-squared statistic and P-value are also presented.

Age (years)	IRR (95% CI)	Chi-squared	P-value
<1	1.30 (1.10-1.50)	7.60	0.00597
1-2	0.86 (0.70-1.00)	2.40	0.12100
2-3	0.73 (0.58-0.91)	8.00	0.00473
3-4	0.90 (0.70-1.20)	0.62	0.43200

The quarterly incidence of ceftriaxone treatment episodes by indication are shown in Figure 7.

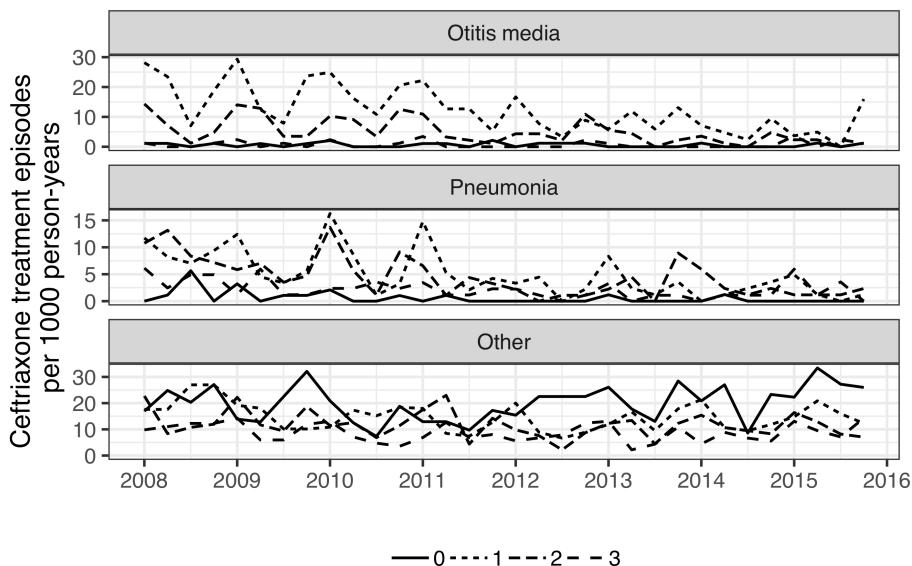


Figure 7. The quarterly incidence rate (IR) of ceftriaxone treatment episodes stratified by age and indication for the period from January 2008 to December 2015. The IR per 1,000 person-years is presented for children one, two, three and four years of age using different line-types. The figure is stratified by indication, and demonstrates a decrease in the IR of ceftriaxone treatment episodes for acute otitis media and pneumonia in the post-vaccine period January 2012 to December 2016. No such decrease is visible for ceftriaxone treatment episodes for all other indications.

To further test whether a general decrease was occurring in the overall use of ceftriaxone, rather than a specific decrease for vaccine-related indications in vaccinated children, an examination of ceftriaxone treatment episodes in all children regardless of age and indication was undertaken. An

overall decrease in the IR of ceftriaxone treatment episodes was found among children under 18 years of age regardless of indication. The IR declined from 11.1 to 9.55 treatment episodes per 1,000 person-years, IRR 0.86 (95% CI 0.81-0.91). The effect was not consistent across age-groups ( $\chi^2 = 23.6$ ,  $P<0.001$ ). When examined by age-group, the overall decrease proved to be driven by the youngest age-group – i.e. the children who were protected by the vaccination. The incidence of ceftriaxone treatment episodes did not decrease significantly in other age groups (Figure 8).

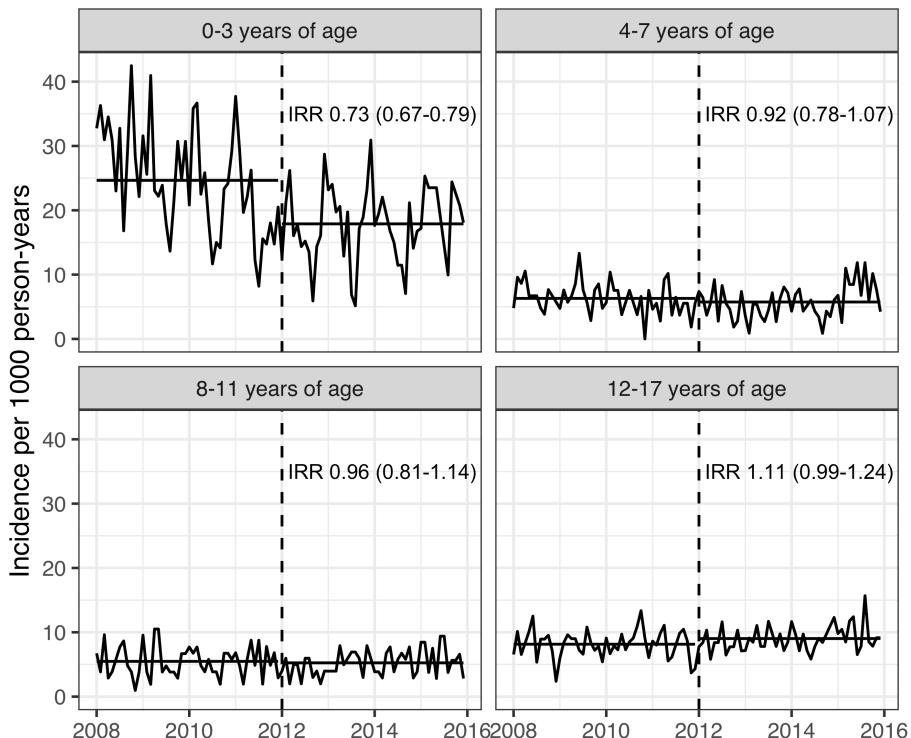


Figure 8. The monthly incidence rates (IR) of ceftriaxone treatment episodes per 1,000 person-years regardless of indication stratified by age-groups for the period from January 2005 to December 2016. The delineation between the pre- and post-vaccine periods on January 2012 is illustrated with a dashed vertical line. For each age-group, the mean IR in the pre- and post-vaccine periods are depicted with a solid horizontal line. The incidence rate ratio (IRR) between the two vaccine periods is shown for each age-group along with 95% confidence intervals within parentheses. The figure demonstrates a significant decrease in the IR of ceftriaxone treatment episodes for children zero to three years of age. No change is detectable in other age-groups.

The demographics of the study birth-cohorts are described in chapter 4.1 and Table 14. A total of 92,935 primary care visits for acute otitis media were recorded among birth-cohorts 2005-2015 during the study period from 1

January 2005 to 31 December 2015. The crude incidence rate of AOM visits to primary care per 100 person-years in the VNEC and VEC was 45.3 and 39.8 respectively. The IR and number of AOM visits by birth-cohort and gender are shown in Table 26.

Table 26. The incidence rate (IR) of acute otitis media visits to primary care physicians for each birth-cohort and gender. The absolute number of visits are presented within parentheses.

Birth-cohort	Females	Males
2005	41.9 (2,777)	49.0 (3,439)
2006	46.1 (3,096)	50.9 (3,605)
2007	45.7 (3,118)	50.3 (3,646)
2008	46.2 (3,259)	45.3 (3,419)
2009	40.9 (2,981)	47.0 (3,649)
2010	45.0 (3,207)	47.0 (3,523)
2011	39.1 (2,631)	44.1 (3,164)
2012	40.6 (2,760)	41.8 (2,977)
2013	38.0 (2,125)	42.8 (2,322)
2014	37.4 (1,200)	44.0 (1,465)
2015	15.8 (157)	20.8 (222)

The lowest incidence was observed in children zero to three months of age, ranging from 3-6 visits per 100 person-years. Thereafter, the incidence increased sharply, and peaked in children eight to eleven and twelve to fifteen months of age, ranging from 50 to 80 visits per 100 person-years. The crude IR decreased significantly in all age-groups, with incidence rate ratios ranging from 0.60 to 0.94. The largest and visually most consistent decrease in incidence was observed among children zero to three months of age, IRR 0.6 (95%CI 0.51 to 0.69), Figure 9.

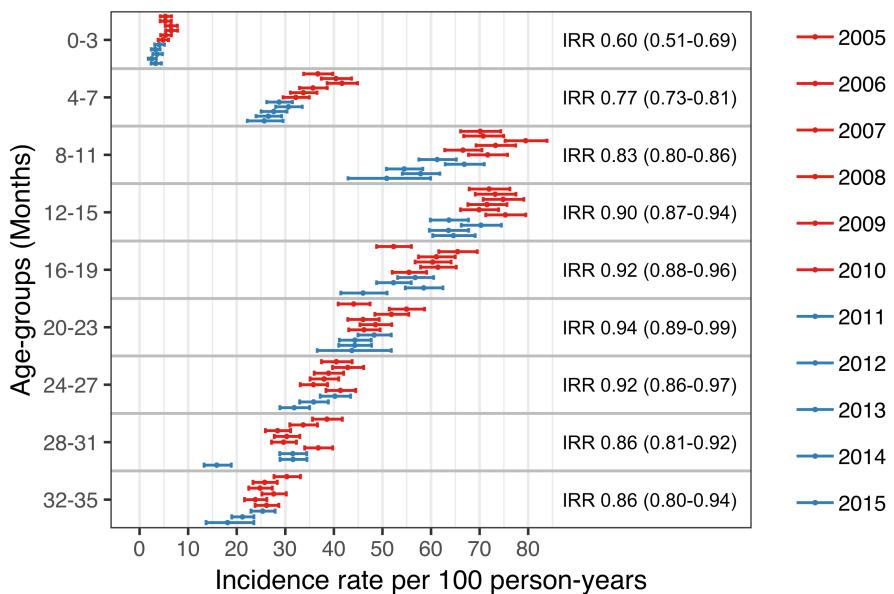


Figure 9. The incidence rate (IR) of acute otitis media (AOM) visits to primary care physicians stratified by birth-cohort and four-month age-groups. The estimated IR is illustrated with a point and 95% confidence intervals are depicted with horizontal error-bars. The vaccine non-eligible birth-cohorts (VNEC) are illustrated in red, and the vaccine eligible birth-cohorts in blue. The incidence rate ratio (IRR) between the VEC and VNEC is shown for each age-group and 95% confidence intervals are presented within parentheses.

When tabulated by the cumulative number of AOM episodes experienced by each child, the proportion of children experiencing zero episodes of AOM increased in the VEC compared to the VNEC, while the proportion experiencing one to four episodes and five or more decreased, as shown in Table 27.

Table 27. The proportion of each vaccine eligibility cohort that experienced zero, one to four and five to twelve cumulative episodes of AOM by 36 months of age. The incidence risk ratio (IRR) between the vaccine eligible cohorts (VEC) and vaccine non-eligible cohorts (VNEC) is presented along with 95% confidence intervals within parentheses.

No. visits	VNEC (%)	VEC (%)	Incidence risk (95%CI)
0	40.0	43.2	1.14 (1.10-1.18)
1-4	55.7	53.2	0.904 (0.876-0.932)
5-12	4.23	3.58	0.84 (0.744-0.946)

Discrimination indices for the Andersen-Gill multiple event model were adequate, Nagelkerke's  $R^2 = 0.110$  and Somer's  $D_{xy} = 0.238$ . No systematic deviations in Schoenfeld residuals were detected on diagnostic plots indicating that the proportional hazard assumption for each covariate were met. There was little variation in the hazard of AOM between vaccine non-eligible birth-cohorts. Only the 2007 birth-cohort differed significantly, with a hazard ratio of 1.06 (95%CI 1.01 to 1.12) compared to the 2010 birth-cohort. An abrupt and significant decrease in the hazard of AOM was noted in the first vaccine eligible cohort, which continued for all remaining VEC (Figure 10). The estimated impact of PHiD-CV10 on AOM episodes in the primary care setting among children younger than three years of age was 21% (95%CI 11% to 30%).

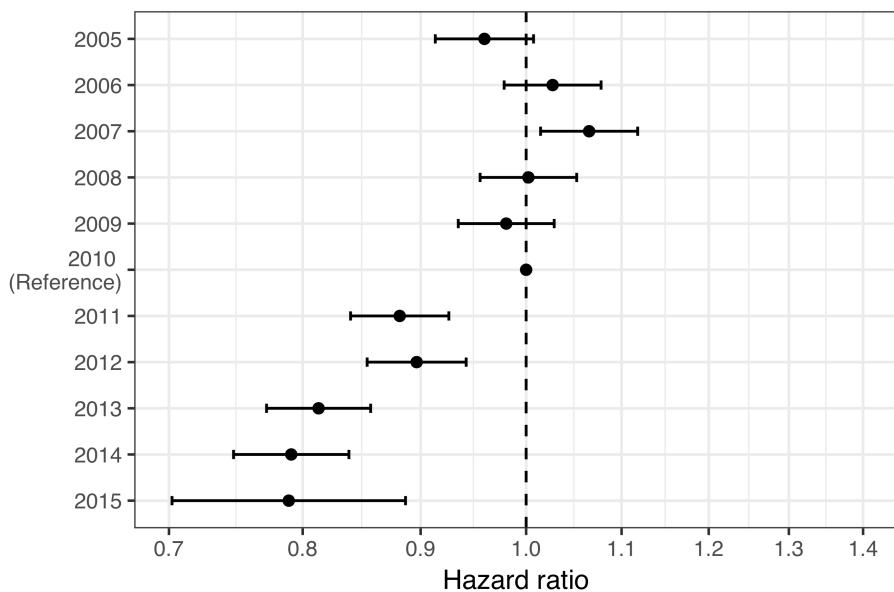


Figure 10. The hazard ratio (HR) of acute otitis media (AOM) between each birth-cohort and the last vaccine non-eligible birth-cohort is shown. The estimated HR is presented with a point, and 95% confidence intervals are illustrated with horizontal error-bars. The 2010 birth-cohort is used as a reference and therefore no confidence intervals are presented. A dashed vertical line is placed on the ratio value of one to assist in visually estimating significance. The X-axis is on the logarithmic scale. The figure demonstrates an abrupt decrease in the hazard of AOM in the first vaccine eligible birth-cohort.

When the hazard ratio of AOM between VEC and VNEC was stratified by the number of previous AOM episodes, the vaccine impact was discernible in children who had experienced either no or only one previous AOM episode.

Among children who had more than one previous AOM episode, no effect was found (Figure 11).

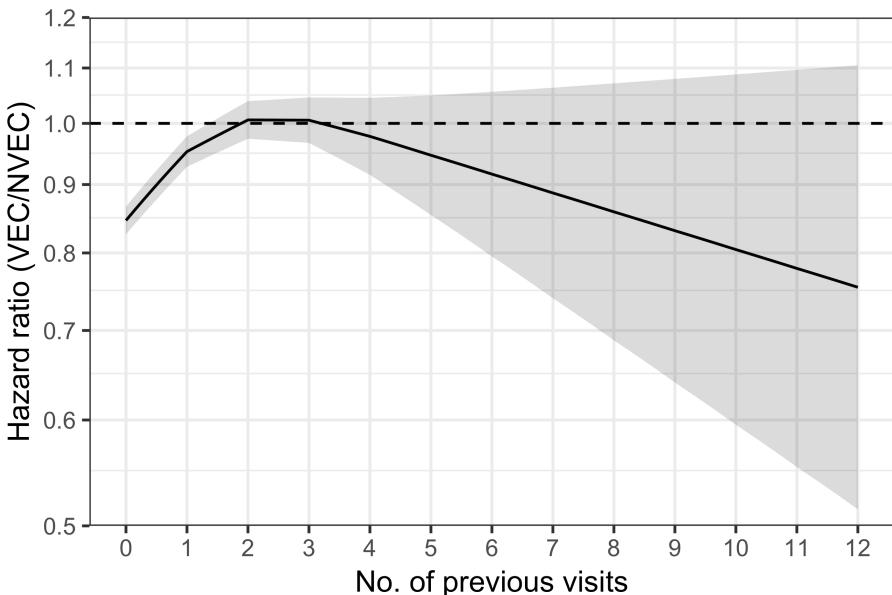


Figure 11. The hazard ratio (HR) of acute otitis media (AOM) between the vaccine eligible (VEC) and vaccine non-eligible cohorts (VNEC) stratified by the number of previous AOM episodes. The estimated HR is illustrated as a solid black line, and 95% confidence intervals are presented as a shaded area. A dashed horizontal line is placed on the ratio value of one to assist in visually assessing significance. The Y-axis is truncated at a HR of 0.5 and is presented on the logarithmic scale. The figure demonstrates a significantly lower hazard of experiencing an additional episode of AOM among vaccine eligible children who have previously experienced zero or one episodes.

The mean number of AOM episodes in primary care was calculated as a function of age using the generalized Nelson-Aalen estimate of the underlying Andersen-Gill model. By their third birthday, the average child in the VNEC had experienced 1.61 episodes of AOM. The average child in the VEC had experienced 1.37. The mean number of AOM episodes by age is shown in Figure 12.

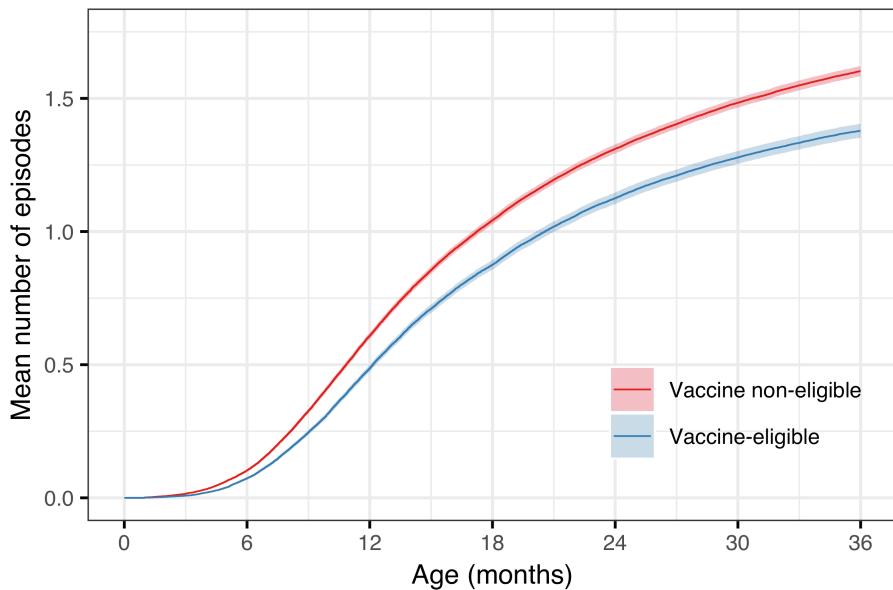


Figure 12. The mean number of acute otitis media (AOM) episodes is shown as a function of age. The estimated mean is presented as a solid red line for the vaccine non-eligible cohorts and a blue line is used for the vaccine eligible cohorts. The 95% confidence intervals are illustrated as shaded areas. The figure demonstrates an early divergence in the mean number of episodes between the two cohorts.

#### 4.3 Impact on outpatient antimicrobial prescriptions (Paper III)

Demographic data regarding the study birth-cohorts are summarized in chapter 4.1 and Table 14. During the study period from 1 January 2005 to 31 December 2016, a total of 276,109 prescriptions were filled for 55,599 Icelandic children under three years of age. From 2005-2012, first-line penicillins were the most commonly prescribed antimicrobials and represented between 41% and 47% of all antimicrobial prescriptions in this age-group. Their use decreased suddenly to 32% in 2013, and represented only 18% of all antimicrobial prescriptions in 2014 and 2015. During this same period, the use of second-line penicillins increased from 35%-40% from 2005-2012, to 48%, 55% and 54% in 2013, 2014 and 2015. Use of cephalosporins followed a similar trend – their use represented between 5.2% and 7.8% of all prescriptions 2005–2012, and increased to 10–15% between 2013–2016. Antimicrobial prescriptions by calendar year are shown in Table 28.

Table 28. The incidence rate (IR) of outpatient antimicrobial prescriptions among children younger than three years of age is shown by calendar-year. Antimicrobials were grouped based on a previously published classification system (Youngster et al. 2017). First-line penicillin includes amoxicillin, dicloxacillin and phenoxymethylpenicillin. Amoxicillin-clavulanate is the only antimicrobial included in the second-line penicillin category and erythromycin is the only first-generation macrolide. Second-generation macrolides include azithromycin and clarithromycin. Cefuroxime and cephalexin are the most common cephalosporins and the category Other includes mostly trimethoprim and trimethoprim and sulfamethoxazole.

Year	IR (n)	Penicillin		Macrolide		Cephalosporin	Other
		1st-line (%)	2nd-line (%)	1st-gen (%)	2nd-gen (%)	(%)	(%)
2005	204 (12,570)	41.4	37.9	1.5	6.5	5.4	7.3
2006	206 (12,844)	40.3	39.6	1.3	6.2	5.4	7.2
2007	192 (13,111)	45.0	36.8	1.6	6.4	5.2	5.1
2008	178 (13,474)	46.7	35.2	0.2	6.4	5.9	5.6
2009	159 (14,062)	46.4	37.2	0.0	5.5	6.3	4.5
2010	167 (14,382)	43.7	38.5	0.0	5.5	7.0	5.2
2011	164 (14,588)	44.7	37.9	0.0	5.9	7.5	4.0
2012	160 (14,225)	43.5	39.0	0.0	6.9	7.8	2.8
2013	152 (13,893)	32.1	48.1	0.0	6.6	10.0	3.2
2014	152 (13,390)	18.5	55.5	0.0	6.6	14.5	4.9
2015	150 (13,284)	18.5	53.9	0.1	7.3	15.0	5.3
2016	160 (12,813)	35.3	41.7	0.0	5.5	12.9	4.6

The proportion of visits resulting in antimicrobial prescription and the incidence of antimicrobial prescriptions linked to each of the study's diagnostic groups are shown in Figure 13. The proportion of otitis media visits resulting in an antimicrobial prescription remained stable at between 57% and 64% of visits. The incidence of otitis media associated prescriptions decreased from a high of 54.9 prescriptions per 100 person-years in 2008 to 39.8 prescriptions per 100 person-years in 2015.

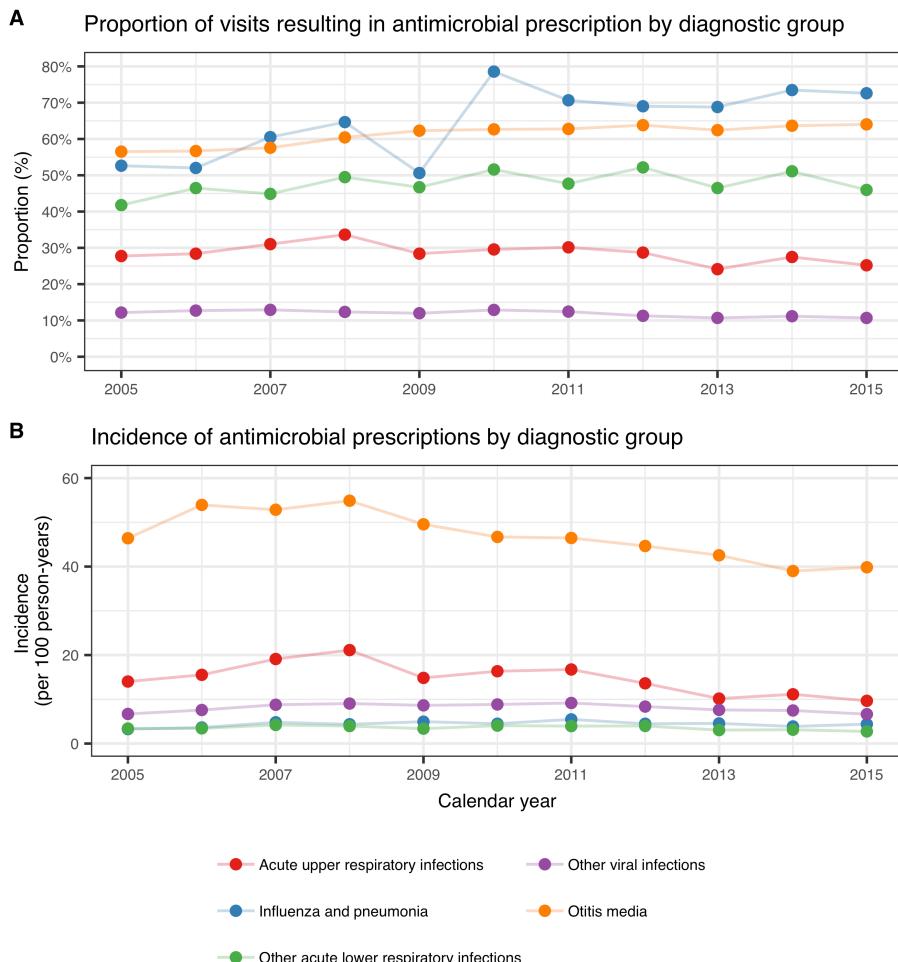


Figure 13. The proportion of visits resulting in antimicrobial prescription and the incidence of prescriptions for each diagnostic group for the period from 2005 to 2015. The diagnostic groups and their corresponding color are presented in the figure legend. The figure demonstrates that the proportion of visits resulting in antimicrobial prescriptions remains fairly stable for most diagnostic groups, while the incidence is decreasing.

During the study period, a total of 226,084 outpatient antimicrobial prescriptions were recorded among birth-cohorts 2005-2015. The crude incidence rate of outpatient antimicrobial prescriptions per 100 person-years in the VNEC and VEC was 164.6 and 150.2 respectively. The incidence rate and number of outpatient antimicrobial prescriptions by birth-cohort and gender is shown in Table 29.

Table 29. The incidence rate (IR) of outpatient antimicrobial prescriptions is presented by birth-cohort and gender. The absolute number of prescriptions are shown within parentheses.

Birth-cohort	Females	Males
2005	176.0 (11,178)	200.0 (13,423)
2006	167.0 (10,843)	190.0 (13,109)
2007	153.0 (10,140)	174.0 (12,339)
2008	153.0 (10,543)	171.0 (12,492)
2009	151.0 (10,699)	169.0 (12,775)
2010	150.0 (10,366)	161.0 (11,854)
2011	142.0 (9,230)	156.0 (10,906)
2012	142.0 (9,447)	158.0 (11,058)
2013	138.0 (9,015)	158.0 (10,180)
2014	145.0 (7,726)	167.0 (9,234)
2015	138.0 (4,075)	173.0 (5,452)

When stratified by six-month age-groups, the lowest incidence was observed in children zero to five months of age and ranged from 30 to 50 prescriptions per 100 person-years. The observed incidence increased sharply thereafter and peaked among children twelve to seventeen months of age, ranging from 225 to 280 prescriptions per 100 person-years. The crude IR decreased significantly in all age-groups, with incidence rate ratios ranging from 0.82 to 0.94 (Figure 14).

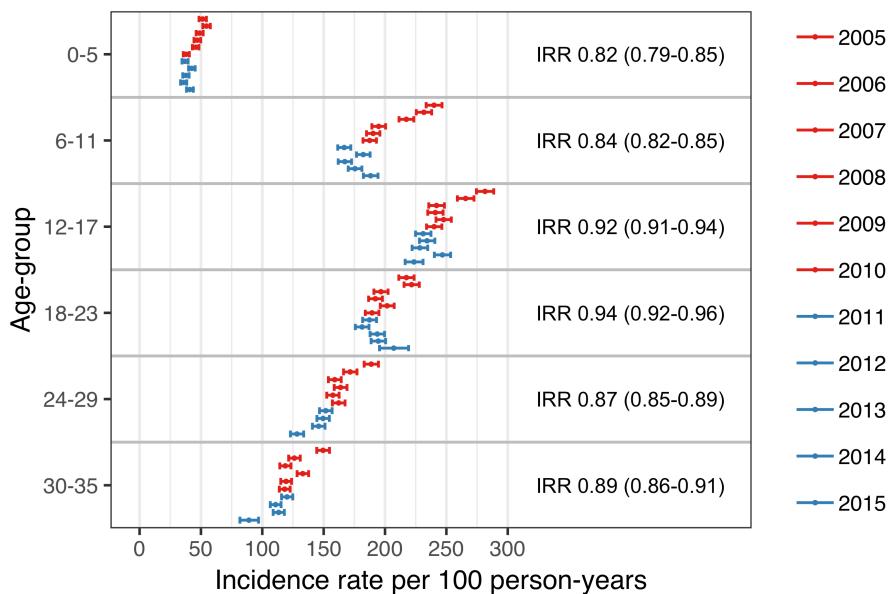


Figure 14. The incidence rate (IR) of outpatient antimicrobial prescriptions is shown stratified by birth-cohort and six-month age-groups. The estimated IR is shown as a point and 95% confidence intervals are illustrated with horizontal error-bars. The vaccine non-eligible cohorts (VNEC) are depicted in red, and the vaccine eligible cohorts (VEC) in blue. The incidence rate ratio (IRR) between the VEC and VNEC is shown for each age-group and 95% confidence intervals are presented within parentheses.

The proportion of children in the VNEC and VEC who filled at least one antimicrobial prescription by three years of age was 88.6% and 86.8% respectively. Children in the VEC were significantly more likely than children in the VNEC not to have filled an antimicrobial prescription (incidence risk ratio 1.16, 95%CI 1.10 to 1.23) or to have filled only between one and four antimicrobial prescriptions (incidence risk ratio 1.08, 95%CI 1.06 to 1.11). The cumulative number of prescriptions by vaccine eligibility cohort is shown in Table 30.

Table 30. The proportion of children in the vaccine non-eligible cohorts (VNEC, 2005–2010) and vaccine eligible cohorts (VEC, 2011–2013) who filled 0, 1–4, 5–9, 10–14 and  $\geq 15$  antimicrobial prescriptions by 36 months of age.

No. prescriptions	VNEC (%)	VEC (%)	Incidence risk (95%CI)
0	11.4	13.2	1.16 (1.10-1.23)
1-4	43.7	47.3	1.08 (1.06-1.11)
5-9	31.6	29.0	0.918 (0.889-0.947)

10-14	9.79	7.52	0.768 (0.716-0.823)
≥15	3.51	2.91	0.831 (0.74-0.934)

Discrimination indices for the Andersen-Gill multiple event model were adequate, Nagelkerke's  $R^2 = 0.212$  and Somer's  $D_{xy} = 0.295$ , and no significant deviations from the model assumptions were visible on diagnostic plots. The model was used to estimate the hazard ratio of outpatient antimicrobial prescriptions between each of the study's birth-cohorts and the last vaccine non-eligible cohort, 2010. Visually, there seemed to be a decreasing trend in hazard of prescription among the vaccine non-eligible birth-cohorts (Figure 15). The hazard did not change significantly between the last vaccine non-eligible birth-cohort and the preceding two cohorts. It did decrease significantly thereafter, with each vaccine eligible cohort having a significantly lower hazard of outpatient antimicrobial prescription. The estimated impact of PHiD-CV10 on outpatient antimicrobial prescriptions among children younger than three years of age was 8% (95%CI 4% to 12%).

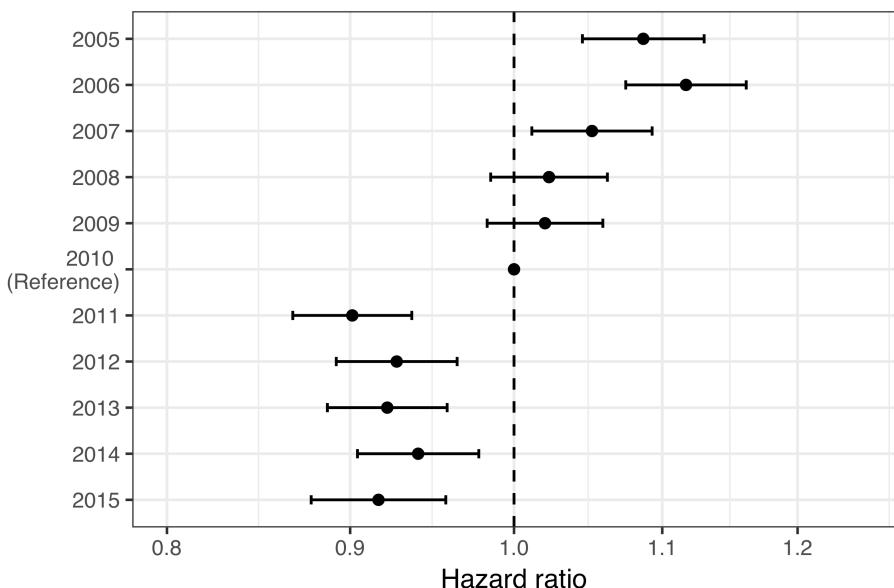


Figure 15. The hazard ratio (HR) of outpatient antimicrobial prescription between each birth-cohort and the last vaccine non-eligible birth-cohort. The estimated HR is depicted as a point, and 95% confidence intervals are illustrated with horizontal error bars. The 2010 birth-cohort is used as a reference and by definition, no uncertainty is present. Therefore, no confidence intervals are presented. A dashed vertical line is placed on the ratio value of one to assist in visually estimating significance. The X-axis is on a logarithmic scale. The figure demonstrates a decreasing trend in the

hazard of outpatient antimicrobial prescription in the vaccine non-eligible cohorts. An abrupt decrease in the hazard is observed in the first vaccine eligible birth-cohort.

When stratified by the number of previous prescriptions, an independent vaccine impact on subsequent prescriptions was still discernible in children who had received up to three prior antimicrobial prescriptions. Among children who had received more than three prior prescriptions, no effect was found (Figure 16).

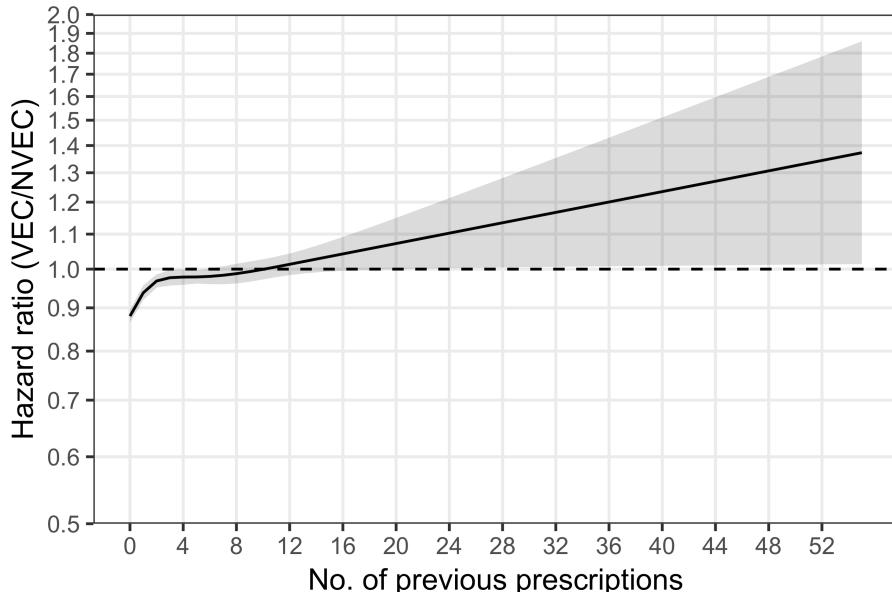


Figure 16. The hazard ratio (HR) of outpatient antimicrobial prescriptions between the vaccine eligible (VEC) and vaccine non-eligible cohorts (VNEC) stratified by the number of previous prescriptions. The estimated HR is depicted as a solid black line, and 95% confidence intervals are illustrated as a shaded area. A dashed horizontal line is placed on the ratio value of one to assist in visually assessing significance. The Y-axis is truncated at a HR of 0.5 and is presented on a logarithmic scale. The figure demonstrates a significantly lower hazard of filling additional outpatient antimicrobial prescriptions among vaccine eligible children who had previously filled fewer than four prescriptions.

The mean number of outpatient antimicrobial prescriptions as a function of age was calculated using the generalized Nelson-Aalen estimate of the underlying Andersen-Gill model. The average male child in the VNEC had filled 6.48 antimicrobial prescriptions by his fourth birthday, and the average female child had filled 6.07. The average male and female children in the VEC had filled 5.84 and 5.46 prescriptions respectively. The mean number of antimicrobial prescriptions by age and gender is shown in Figure 17.

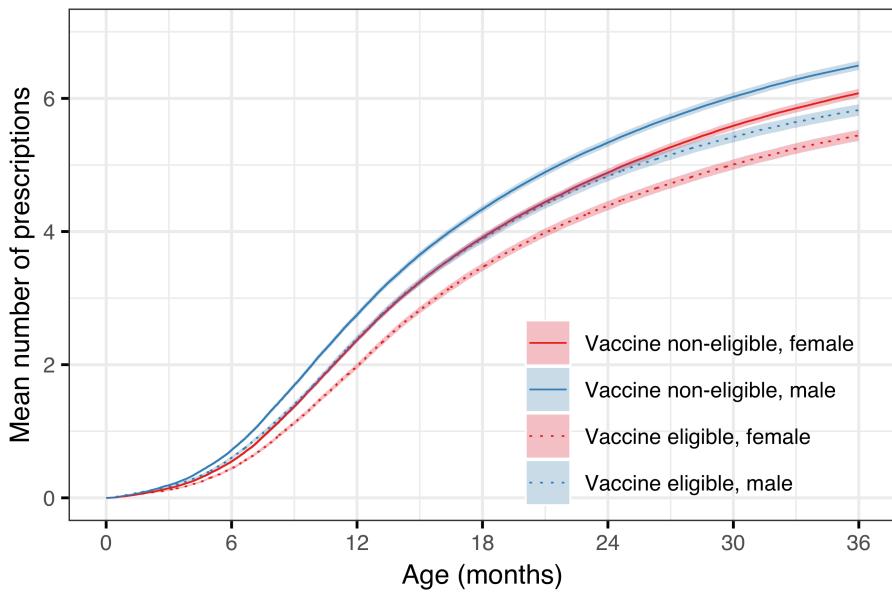


Figure 17. The mean number of outpatient antimicrobial prescriptions are shown as a function of age, and stratified by vaccine eligibility cohort and gender. The figure deviates from the color schema used in other figures that compromise this thesis. Here, the estimates for females are illustrated in red and males in blue. Vaccine non-eligible cohorts are represented with solid lines and vaccine eligible cohorts with dashed lines. The 95% confidence intervals are illustrated as shaded areas. The figure demonstrates an early divergence in the mean number of prescriptions, and a consistent difference between genders.

#### 4.4 Impact on tympanostomy tube procedures (Paper IV)

Demographic data regarding the study birth-cohorts are summarized in chapter 4.1. In total, during the study period from 1 January 2005 to 31 December 2016, 14,351 children underwent 20,373 tympanostomy tube placements, 57% of whom were male.

The median age of children undergoing their first tympanostomy procedure was 17 months (IQR 13-24, 18% younger than one year of age). In the subset of children who underwent a TTP during the study period, 10,248 (71%) underwent only one procedure, 2,902 (20%) underwent two, and 1201 (8%) underwent three or more. Almost all (98%) of the procedures were performed in private outpatient clinics. The number of otolaryngologists performing outpatient TTP increased from 15 in 2005 to 23 in 2016. Each surgeon performed a median of 123 (IQR: 56.5-196) procedures each year. The study's population is summarized in Table 31.

Table 31. An overview of the birth-cohorts included in paper IV. The number of observed tympanostomy tube placements (TTP) in each cohort is presented, with the number of children undergoing the procedures within parentheses. The median age in months at the time of a child's first procedure is shown along with the interquartile range. The observational period is 1 January 2005 to 31 December 2016. Birth-cohorts 2012-2015 do not attain full follow-up time, as indicated by fewer person-years included in the study. Thus, the decrease in the number of procedures and median age in those cohorts is not indicative of a true decrease. These cohorts are colored with darker gray banded rows for emphasis.

Birth-cohort	Number of children	Person-years	Number of procedures (n children)	Median age (months)
2005	4,541	21,409	1,946 (1,280)	17 (12-25)
2006	4,665	21,988	1,931 (1,303)	18 (13-27)
2007	4,770	22,500	1,974 (1,335)	18 (13-27)
2008	4,949	23,313	2,140 (1,428)	18 (13-26)
2009	5,128	24,141	2,145 (1,514)	18 (13-25)
2010	4,984	23,580	2,203 (1,547)	18 (13-26)
2011	4,642	22,056	1,997 (1,382)	18 (13-24)
2012	4,668	20,195	2,057 (1,419)	16 (12-23)
2013	4,442	14,964	1,642 (1,200)	16 (13-23)
2014	4,444	10,744	1,582 (1,251)	16 (13-20)
2015	4,136	5,983	756 (692)	13 (11-15)

The crude incidence rate of TTP in the vaccine eligible cohorts was 10.6 procedures per 100 person-years. This was significantly higher than the crude incidence rate in the vaccine non-eligible cohorts, 8.7 procedures per 100 person-years (IRR 1.20, 95%CI 1.17 to 1.24). When stratified by age-groups, the crude incidence rate was highest among 12-17 month old children, ranging from 19 to 27 procedures per 100 person-years (Figure 18).

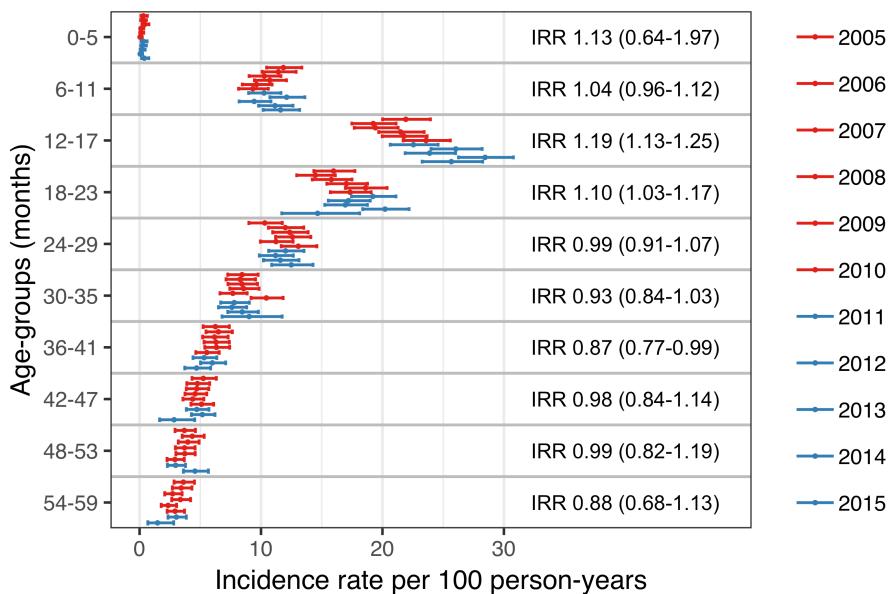


Figure 18. The incidence rate (IR) of tympanostomy tube placements (TTP) stratified by birth-cohort and six-month age-groups. The estimated IR is represented with a point, and 95% confidence intervals are illustrated with horizontal error-bars. The vaccine non-eligible cohorts (VNEC) are depicted in red, and the vaccine eligible cohorts (VEC) in blue. The incidence rate ratio (IRR) between the VEC and VNEC is shown for each age-group and 95% confidence intervals are presented within parentheses.

The cumulative incidence of children who had undergone at least one TTP by five years of age was highest in birth-cohort 2010 (31.7%), and lowest in birth-cohort 2006 (28.6%), Table 32. The cumulative incidence of tympanostomy procedures was significantly higher in the VEC compared to VNEC regardless of age (Figure 19).

Table 32. The cumulative incidence of having undergone at least one tympanostomy tube placement (TTP) at six-month age intervals is presented. Birth-cohorts 2006 and 2008 are removed because of lack of space. Their absence is indicated by an ellipsis (...). The cumulative incidence is presented as a percentage (%) of all children in the respective cohort. Birth-cohorts 2012-2015 do not attain full follow-up time. Lack of information due to censoring is indicated with a hyphen (-).

Age	2005...	2007...	2009	2010	2011	2012	2013	2014	2015
6	0.4	0.4	0.3	0.1	0.4	0.2	0.3	0.2	0.5
12	7.2	6.6	6.5	6.6	6.6	7.8	6.5	6.9	7.6
18	16.4	14.9	15.7	16.5	16.3	18.3	16.3	19.1	18.4

24	21.1	19.7	22.0	22.4	23.3	23.9	21.7	26.1	-
30	23.7	23.4	25.1	26.3	26.3	26.7	24.9	29.0	-
36	25.8	25.3	27.2	28.8	27.9	28.3	26.9	-	-
42	26.9	26.7	28.5	30.1	28.7	29.5	27.5	-	-
48	27.8	27.8	29.1	31.0	29.4	30.4	-	-	-
54	28.4	28.4	29.9	31.4	30.1	30.9	-	-	-
59	28.8	28.6	30.2	31.7	30.4	31.3	-	-	-

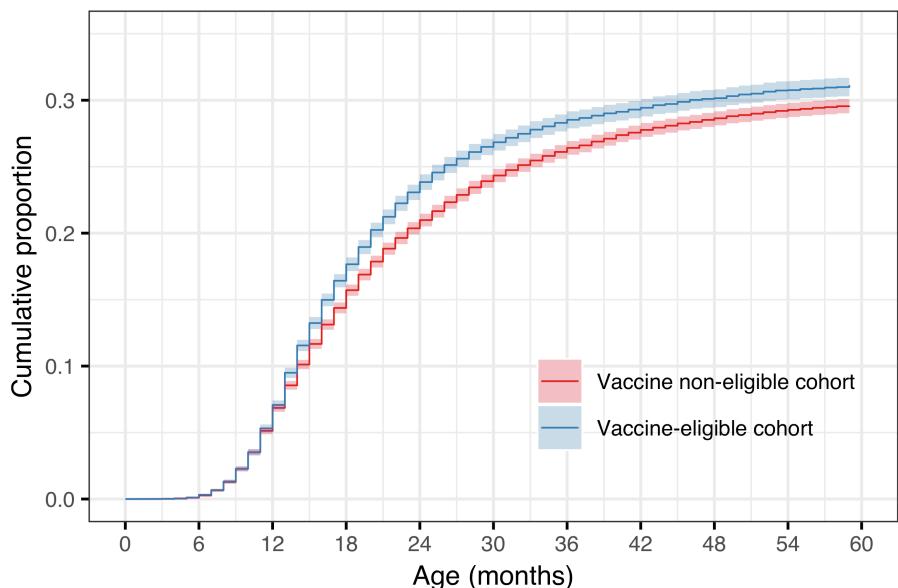


Figure 19. The cumulative incidence of tympanostomy tube placements (TTP) is shown for the vaccine eligible (VEC) and vaccine non-eligible cohorts (VNEC) as a continuous function of age. Cumulative incidence is presented as a proportion of all children in the respective vaccine eligibility cohort. The estimated cumulative incidence is illustrated with a solid red line for the VNEC, and a solid blue line for the VEC, and 95% confidence intervals are depicted with a shaded area.

In the subset of children who underwent TTP, the mean (median) number of otitis media associated visits to primary care or to the pediatric emergency department was 2.05 (2) visits in the vaccine non-eligible cohorts, compared to 1.72 (1) visits in the vaccine eligible cohorts. The distribution in the number of previous visits was significantly different between the VNEC and VEC (Chi-Squared test statistic 63.8, P<.001). The proportion of children who did not have a single recorded visit prior to undergoing the procedure increased from 20.6% in the VNEC to 28.9% in the VEC, RR 1.40 (95%CI 1.28-1.54).

Children in the vaccine eligible cohorts had received significantly fewer antimicrobial prescriptions prior to undergoing the procedure (Chi-Squared test statistic 53.6, P<.001). The mean (median) number of previous antimicrobial prescriptions was 3.19 (4) in the vaccine eligible cohorts compared to 3.62 (4) in the vaccine non-eligible cohorts. Children in the VEC were more likely to have never been prescribed antimicrobials prior to undergoing tympanostomy placement, RR 1.52, 95%CI 1.18-1.96). The comparison between VEC and VNEC is summarized in Tables 33 and 34.

Table 33. The cumulative number of previous antimicrobial prescriptions for those children in the vaccine non-eligible (VNEC) and vaccine eligible cohorts (VEC) who underwent at least one tympanostomy tube placement. The proportion of each cohort who had the corresponding number of previous prescriptions is shown with the absolute number of children within parentheses. The relative risk (RR) and absolute risk difference (ARD) between the VEC and VNEC is shown with 95% confidence intervals.

Cum. presc.	VNEC % (n)	VEC % (n)	RR (95%CI)	ARD (95%CI)
0	3.4 (286)	5.2 (72)	1.18 (1.52 to 1.96)	1.79 (0.51 to 3.07)
1	11.6 (966)	12.8 (177)	0.95 (1.11 to 1.29)	1.26 (-0.68 to 3.19)
2	19.3 (1,610)	22.6 (311)	1.05 (1.17 to 1.30)	3.28 (0.87 to 5.68)
3-4	37.8 (3,150)	37.4 (516)	0.92 (0.99 to 1.07)	-0.39 (-3.19 to 2.41)
5-7	22.3 (1,860)	19.3 (266)	0.77 (0.86 to 0.97)	-3.01 (-5.32 to -0.70)
8+	5.6 (468)	2.7 (37)	0.34 (0.48 to 0.67)	-2.93 (-3.95 to -1.90)

A diagnostic plot of Schoenfeld residuals did not reveal deviations from the proportional hazard's assumption. The hazard of undergoing TTP was considerably higher in children who had previously visited a physician for otitis media or received an antimicrobial prescription.

Table 34. The cumulative number of previous otitis media visits for those children in the vaccine non-eligible (VNEC) and vaccine eligible cohorts (VEC) who underwent at least one tympanostomy tube placement. The proportion of each cohort who had the corresponding number of prior visits is shown with the absolute number of children

within parentheses. The relative risk (RR) and absolute risk difference (ARD) between the VEC and VNEC is shown with 95% confidence intervals.

Cum. visit	VNEC % (n)	VEC % (n)	RR (95%CI)	ARD (95%CI)
0	20.6 (1,720)	28.9 (398)	1.28 (1.40 to 1.54)	8.29 (5.7 to 10.9)
1	24.9 (2,080)	24.4 (337)	0.89 (0.98 to 1.09)	-0.45 (-2.94 to 2.04)
2	20.4 (1,700)	19.6 (270)	0.85 (0.96 to 1.07)	-0.86 (-3.17 to 1.45)
3-4	24.9 (2,080)	20.2 (279)	0.73 (0.81 to 0.91)	-4.64 (-7.0 to -2.29)
5-7	8.0 (666)	6.5 (89)	0.65 (0.81 to 1.00)	-1.53 (-2.99 to -0.07)
8+	1.3 (104)	0.4 (6)	0.15 (0.35 to 0.79)	-0.81 (-1.28 to -0.35)

Children who had one prior documented visit were considerably more likely to undergo the procedure than children who had no documented visits, HR of 3.12 (95%CI 2.93 to 3.32). Likewise, children who had previously filled one antimicrobial prescription were more likely to receive a tympanostomy tube than children who had received no prescription, 6.98 (95%CI 6.13 to 7.95). The hazard of tympanostomy tube placement increased gradually from birth-cohort 2005 to 2015 (Figure 20).

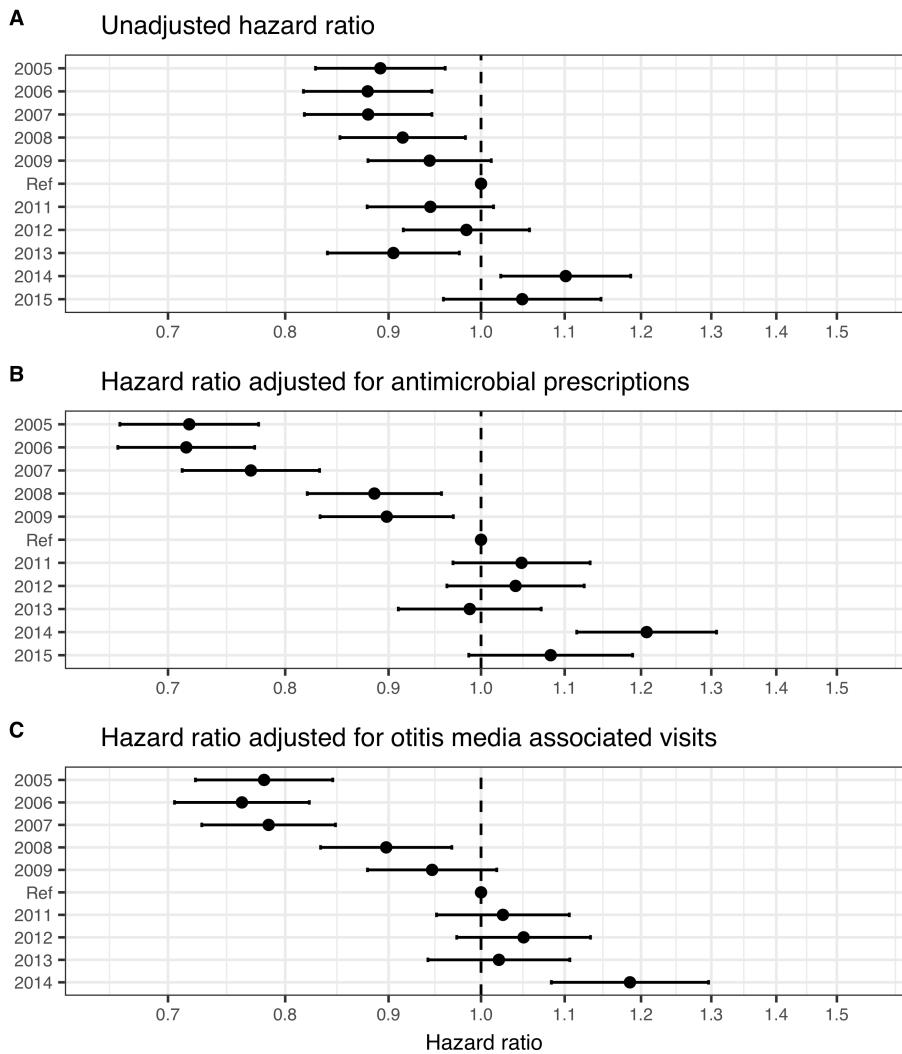


Figure 20. The hazard ratio (HR) of tympanostomy tube placements (TTP) is depicted between each birth-cohort and the last vaccine non-eligible birth-cohort, as estimated by three Cox regression models. In panel A, the unadjusted HR estimates are shown. Panel B shows HR estimates adjusted for antimicrobial prescriptions, and panel C illustrates the HR estimates adjusted for otitis media associated visits. Primary care visits are obtained from the Primary Care Registry of the Directorate of Health, and the observation period is restricted to December 2015. Because of this the data presented in panel C is restricted to birth-cohorts 2005-2014. The figure demonstrates an increasing hazard of TTP with each successive birth-cohort. The effect is more pronounced when adjustment is made for antimicrobial prescriptions and visits.

## 4.5 Impact on respiratory associated hospitalizations (Paper V)

Demographic data regarding the study birth-cohorts are summarized in chapter 4.1. In total, 51,264 children were followed for a median of 1,096 days (range 6-1,096) resulting in 142,315 person-years of follow-up time. Of those, 1,414 children were admitted to hospital 1,703 times with diagnoses compatible with the study's diagnostic groups. The total number of hospital admissions regardless of indication was 4,842. An overview of the demographic data is presented in Table 35.

Table 35. An overview of the birth-cohorts included in paper V. The total number of hospitalizations, hospital admissions due to the study's diagnoses, and admissions to the intensive care unit (ICU) are presented. The number of children is presented within parentheses. The proportion of all hospital admissions that were due to the study's diagnoses is shown. The observational period is 1 January 2005 to 31 December 2017. Birth-cohorts 2014 and 2015 do not attain full follow-up time, as indicated by fewer person-years included in the study.

Birth-cohort	No. children (person-years)	All cause admissions	Study admissions, n (children)	Prop. due to study diagnoses, %	ICU, n (children)
2005	4,541 (13,277)	446	219 (160)	49.1	7 (7)
2006	4,668 (13,658)	415	176 (140)	42.4	10 (8)
2007	4,770 (13,985)	423	186 (160)	44.0	6 (5)
2008	4,953 (14,472)	442	117 (101)	26.5	5 (4)
2009	5,130 (14,965)	484	124 (109)	25.6	7 (6)
2010	4,988 (14,592)	384	158 (138)	41.1	7 (7)
2011	4,644 (13,640)	392	129 (112)	32.9	4 (4)
2012	4,668 (13,753)	576	196 (155)	34.0	0 (0)
2013	4,442 (13,044)	472	149 (119)	31.6	9 (8)
2014	4,446 (10,930)	431	144 (122)	33.4	6 (5)
2015	4,136 (6,140)	377	105 (98)	27.9	3 (3)

Of the children in the study birth-cohorts, 550 were hospitalized 660 times with ICD-10 discharge diagnoses consistent with pneumonia. In the same cohorts, 508 children were admitted 550 times with diagnoses consistent with other acute lower respiratory tract infections. In the vaccine non-eligible cohorts, the crude incidence rate of pneumonia requiring hospital admission

was 4.94 per 1,000 person-years, which decreased to 4.18 per 1,000 in the vaccine eligible cohorts. The analogous crude incidence rate of hospitalizations for other acute lower respiratory tract infections was 2.94 and 5.23 per 1,000 person-years. Though the absolute number of admissions was similar between these two groups, the distribution of cases was different. The crude incidence rate of hospital admissions for pneumonia was highest in children 12-17 months of age, while the incidence rate of hospitalizations for other lower respiratory tract infections was highest in children <6 months of age (Figure 21). Children admitted for other acute lower respiratory tract infections were significantly younger than children admitted for pneumonia (mean age 8.0 months and 13.6 months respectively,  $P<.001$ ). Using crude age-group stratified incidence rate ratios between the vaccine eligible and non-eligible cohorts, the incidence rate of pneumonia hospitalizations was found to have decreased significantly only among children 12-17 months of age, crude incidence rate ratio 0.52 (95%CI: 0.35-0.77). Using the same method, the incidence rate of hospital admissions for other acute lower respiratory tract infections admissions was found to have increased significantly among children 0-5 months of age, crude incidence rate ratio 1.50 (95%CI 1.23-1.84).

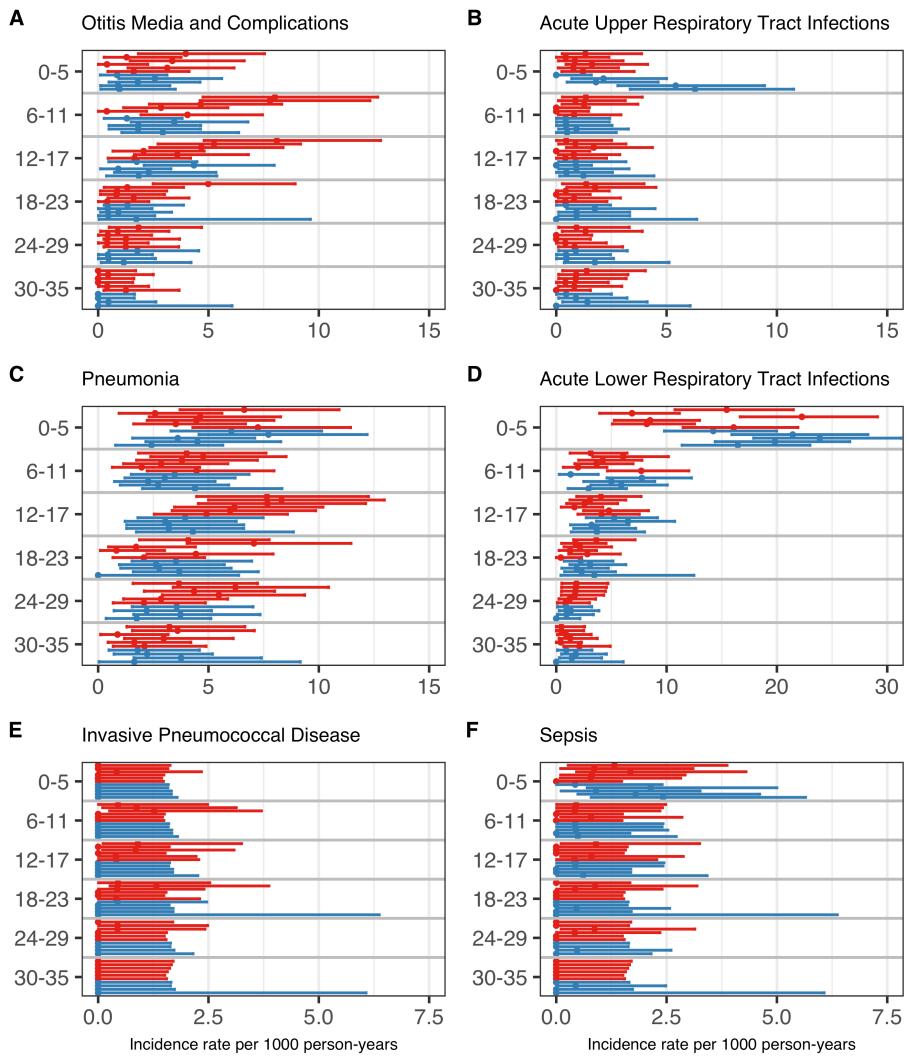


Figure 21. Crude incidence rates (IR) of the six diagnostic groups (A-F) per 1,000 person-years for each of the birth-cohorts. Panels A-D and F depict the IR of admissions based on the International Classification of Diseases, 10th revision (ICD-10) discharge diagnoses, while panel E depicts the IR of admissions with culture confirmed invasive pneumococcal disease (IPD), regardless of ICD-10 diagnosis. Birth-cohorts are compared in six-month age-groups which are illustrated on the Y-axis. The vaccine non-eligible cohorts (VNEC) are illustrated in red and the vaccine eligible cohorts (VEC) in blue.

A significant difference was detected in the cumulative rate of hospital admissions for both pneumonia and acute lower respiratory tract infections between the vaccine eligible and non-eligible cohorts (Figure 22). The hazard ratio of hospital admission for pneumonia was 0.80 (95%CI:0.67-0.95), with

an E-value of 1.81 and a lower bound of 1.29. When the risk-set was restricted to children younger than 90 days and 90 days and older, respectively, the hazard ratio was 1.22 (95%CI 0.81-1.85) and 0.73 (95%CI 0.60-0.89) respectively. The hazard ratio for hospital admission due to acute lower respiratory tract infection was 1.32 (95%CI:1.14-1.53), with an E-value of 1.97 and a lower bound of 1.54. The hazard ratio was augmented when children younger than 90 days were analyzed separately, HR 1.54 (95%CI 1.23-1.94). It was not significant in children 90 days and older, HR 1.18 (95%CI 0.97-1.44).

A total of 131 hospitalizations for acute upper respiratory tract infections were recorded for 123 children. During the same period, 256 children were admitted to hospital 280 times for otitis media and complications. The crude incidence rate of hospital admissions for otitis media was higher than the incidence rate of admissions for acute upper respiratory tract infections; 2.32 and 1.45 per 1,000 person-years in the vaccine eligible and vaccine non-eligible cohorts respectively, compared to 0.78 and 1.13 per 1,000 person-years. The mean age of children admitted for acute upper respiratory tract infections was 13.5 months compared to 12.8 months for children admitted for otitis media and complications. The crude incidence rate by age-group is shown in Figure 21. The cumulative incidence rate of hospitalization per 1000 person-years for acute upper respiratory tract infections and otitis media and complications are shown in Figure 22. The hazard ratio of otitis media hospitalizations between the vaccine eligible and non-eligible cohorts was 0.57 (95%CI:0.43-0.73) with an E-value of 2.9 .and a lower bound of 2.08. When restricted to children younger than 90 days of age, the hazard ratio was 0.72 (95%CI 0.33-1.57), and when evaluating children 90 days and older it was 0.55 (95%CI 0.42-0.72). The hazard ratio for hospital admission for acute upper respiratory tract infections was 1.56 (95%CI:1.11-2.19), with an E-value of 2.49 and a lower bound of 1.46. Among children younger than 90 days, and 90 days and older respectively, the hazard ratio was 3.4 (95%CI 1.72-6.90) and 1.13 (95%CI 0.75-1.71).

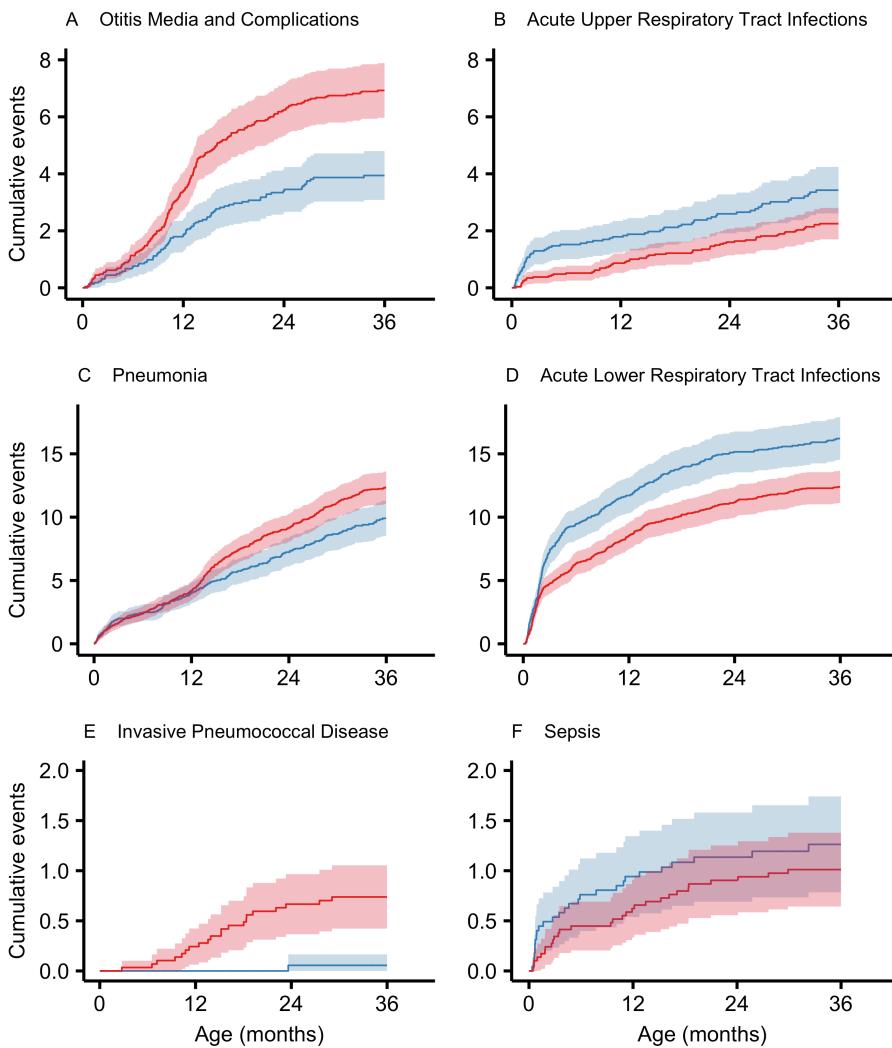


Figure 22. Kaplan-Meier cumulative event curves per 1,000 person-years for each of the diagnostic groups. The vaccine non-eligible cohorts (VNEC) are illustrated in red and the vaccine eligible cohorts (VEC) in blue. The 95% confidence intervals are represented with a shaded area. The Y-axis is scaled independently for each pair of diagnostic groups (A-B, C-D and E-F).

A total of 15 children were admitted to hospital 19 times for meningitis, and 61 children were admitted 63 times for sepsis. The crude incidence rate of meningitis hospitalization was 16.5 and 8.7 per 100,000 person-years in the vaccine non-eligible and vaccine eligible cohorts respectively, and the analogous crude incidence rate for sepsis hospitalizations was 38.8 and 52.3. Culture confirmed invasive pneumococcal disease was diagnosed in 37

children under three years of age in the study birth-cohorts. Of those, 23 (59%) were admitted for inpatient treatment. Of the admitted children, eight children had a primary discharge diagnosis of Sepsis due to Streptococcus pneumoniae (A40.3), eight were diagnosed with Pneumococcal meningitis (G00.1), two with Pneumonia due to Streptococcus pneumoniae (J13), two with Bacterial pneumonia, not elsewhere classified (J15) and the remaining three were diagnosed with Bacterial meningitis, unspecified (G00.9), Pyogenic arthritis, unspecified (M00.9) and Fever, unspecified (R50.9). The crude incidence of invasive pneumococcal disease, regardless of whether the child was admitted to hospital, was 24.7 per 100,000 person-years in the VNEC compared to 1.74 per 100,000 person-years in the VEC. When only considering hospitalized invasive pneumococcal disease, the crude IR was 24.7 and 1.74 per 100,000 person-years. No vaccine-type invasive pneumococcal disease was diagnosed in the VEC. Crude incidence rates of hospitalization by age-group are shown in Figure 21.

Table 36. Hazard ratios (HR) between the vaccine eligible (VEC) and vaccine non-eligible birth-cohorts (VNEC) for each disease-group. A HR lower than one indicates a relative decrease in disease-group in the VEC compared to the VNEC, while a HR higher than one indicates an increase. A HR was not calculated for vaccine-type invasive pneumococcal disease as not cases were diagnosed and the VEC.

Disease group	Hazard ratio (95%CI)
Otitis Media and Complications	0.56 (0.44-0.73)
Acute upper respiratory infection	1.55 (1.10-2.18)
Pneumonia	0.80 (0.67-0.95)
Acute Lower Respiratory Tract Infections	1.32 (1.14-1.53)
Sepsis	1.26 (0.74-2.12)
Invasive Pneumococcal Disease	0.07 (0.01-0.50)

The mean age of children admitted for meningitis, sepsis and invasive pneumococcal disease was 9.7 months, 8.4 months and 14.4 months respectively. The cumulative incidence rates of hospitalization per 1000 person-years for sepsis and invasive pneumococcal disease are depicted in Figure 22. The hazard ratio of hospitalization for meningitis between the vaccine eligible and non-eligible cohorts was 0.45 (95%CI 0.15-1.41). An E-value was not computed as the hazard ratio was not significant. The hazard ratio for hospital admissions due to invasive pneumococcal disease between the vaccine eligible and vaccine non-eligible cohorts was 0.07 (95%CI:0.01-0.50), with an E-value of 28.06. and a lower bound of 3.41. The hazard ratio

of a sepsis hospitalization between the vaccine eligibility cohorts was 1.26 (95%CI:0.75-2.13). No E-value was calculated as the ratio was not significant. Restricted analyses in these three diagnostic groups did not alter results significantly.

## **4.6 Impact and cost-effectiveness analysis (Paper VI)**

### **4.6.1 Population impact on acute otitis media among children younger than 20 years of age**

From 1 January 2005 to 31 December 2015, children younger than 20 years of age visited primary care physicians 164,453 times for acute otitis media and its complications. Strong seasonal variation was detected, with more visits occurring in December through March, and few visits occurring in June and July (Panels A and B of Figure 23). The monthly number of AOM visits during the post-vaccine period was lower than average in all age-groups (Panel B of Figure 23). Though visits regardless of diagnosis also decreased during the post-vaccine period (Panel C of Figure 23), the degree by which visits for AOM decreased was larger in magnitude.

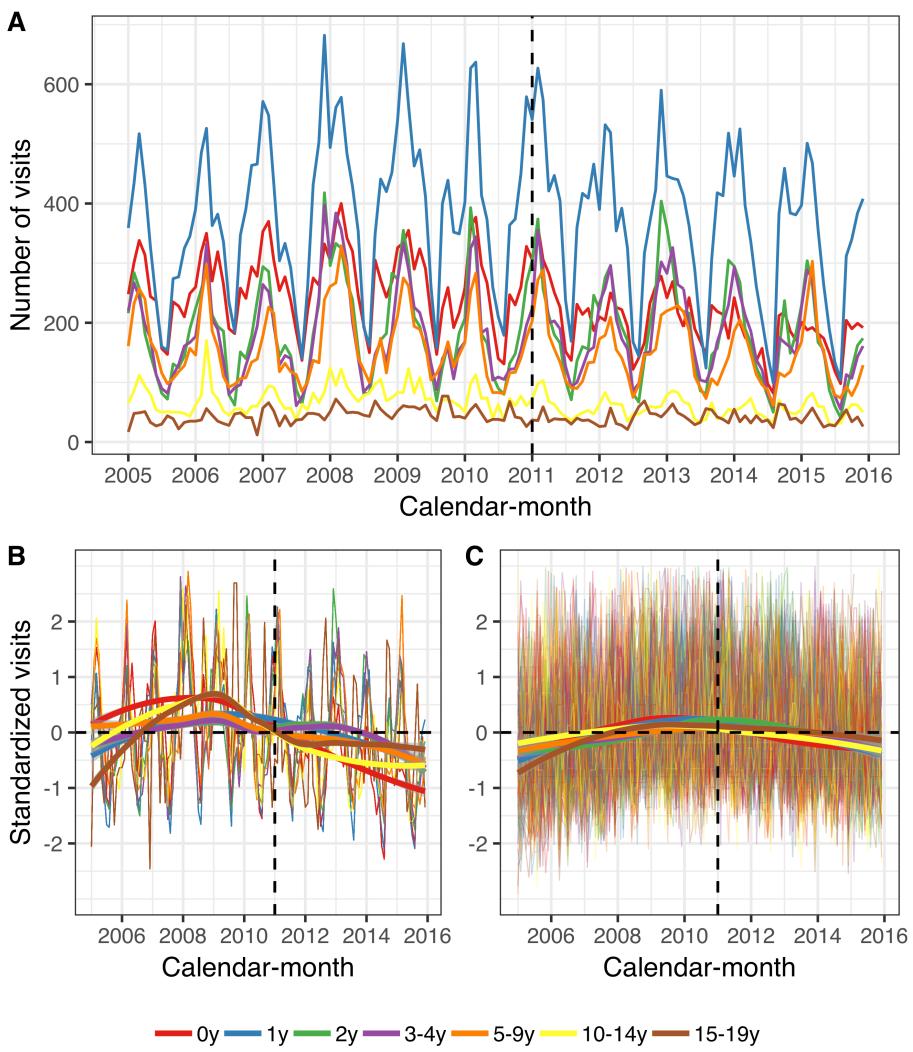


Figure 23. The number of primary care visits among children younger than 20 years of age per calendar-month from 1 January 2005 to 31 December 2015. Children are divided into seven age-groups, listed in the figure legend. Panel A shows the monthly number of visits due to acute otitis media and its complications (AOM). Panels B and C, depict the standardized monthly number of AOM visits (Panel B) and all other visits (Panel C) per age-group. The Y-axis represents the number of standard deviations the observed visits are from the mean of the entire period for each diagnosis and age-group. The horizontal dotted lines represent values that are zero standard deviations from the mean and the vertical dotted lines represent the beginning of the vaccine intervention. Locally estimated scatter-plot smoothing (LOESS) is used to produce an average trend. Panels B and C suggest that the number of both AOM visits and all other visits have decreased in the post-vaccine period, and that AOM visits have decreased to a larger degree.

The posterior predictions of the component models are shown in Figure 24. Each posterior prediction is based on the median of the corresponding marginal posterior predictive distribution. The ITS model with offset consistently predicted the fewest visits in the post-vaccine period. The ITS model without offset consistently predicted the highest number of visits.

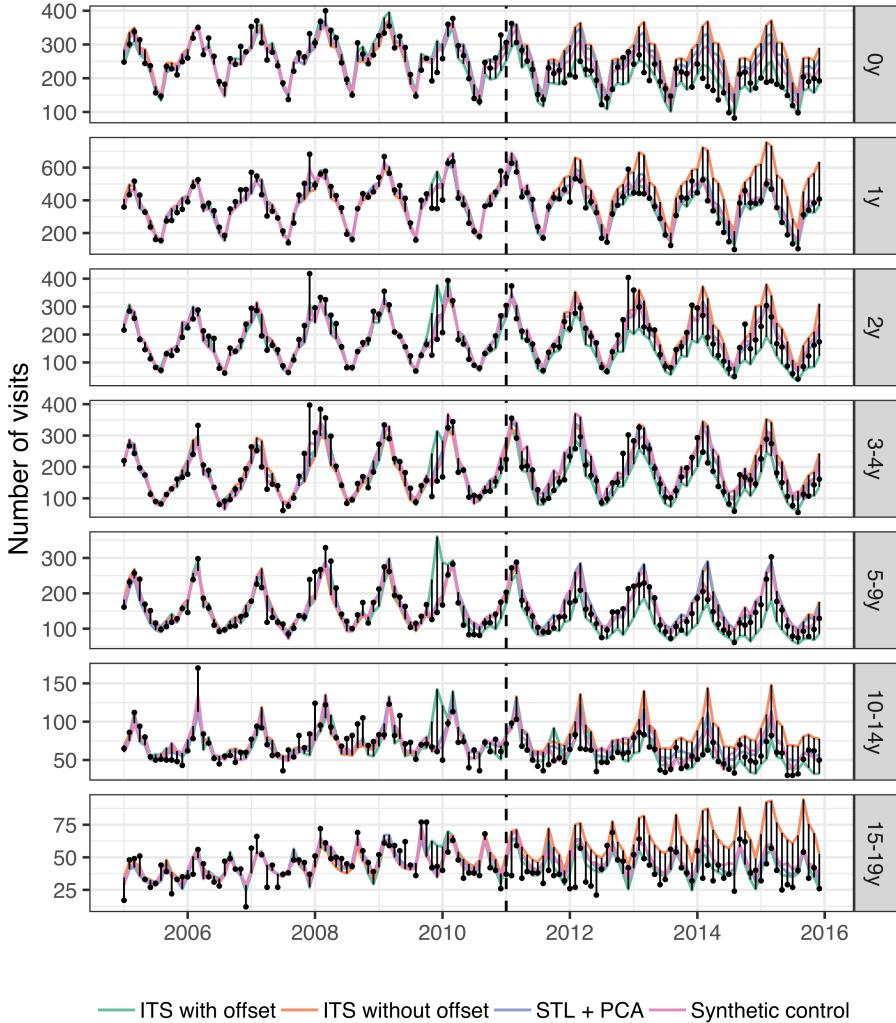


Figure 24. The observed and predicted number of visits for acute otitis media and its complications (AOM) from 1 January 2005 to 31 December 2015 for each age-group. Observed visits are illustrated as black points and the predicted number of visits are drawn as lines for each of the component models. The start of the vaccine period is delineated with a vertical black dotted line. Each component model was fitted to the observed visits in the pre-vaccine period, and then used to predict the number of visits in the post-vaccine period, had the vaccine not been introduced. The distance

between the observed and predicted visits for each calendar-month is depicted with a thin black line. Longer distances suggest a larger discrepancy. Note that the scale of the Y-axis differs between age-groups.

These component models were stacked using LOOCV to produce the final stacked model. The weights used to stack the component models are shown in Table 37.

Table 37. The weights used to produce the final stacked model from the component models. The weights for each component model were obtained by minimizing the leave-one-out mean squared error.

Disease category	Age-group	Synthetic controls	ITS with offset	ITS without offset	STL + PCA
AOM visits	0y	0.221	0.000	0.121	0.659
	1y	0.149	0.000	0.610	0.241
	2y	0.000	0.000	0.479	0.521
	3-4y	0.661	0.000	0.339	0.000
	5-9y	0.726	0.000	0.274	0.000
	10-14y	1.000	0.000	0.000	0.000
	15-19y	0.018	0.000	0.078	0.904
Pneumonia hospitalizations	0-4y	0.912	0.001	0.087	0.000
	5-19y	1.000	0.000	0.000	0.000
	20-39y	0.246	0.124	0.000	0.629
	40-64y	0.241	0.000	0.000	0.759
	65-79y	0.000	0.934	0.066	0.000
	80+	0.000	0.472	0.528	0.000
	IPD hospitalizations	0-4y	0.001	0.999	0.000
	5-64y	1.000	0.000	0.000	0.000
	65y+	1.000	0.000	0.000	0.000

The posterior predicted AOM visits and 95% credible intervals are shown in Figure 25. With few exceptions, the observed number of AOM visits are fewer than predicted in the post-vaccine period, indicating that the vaccine prevented visits from occurring.

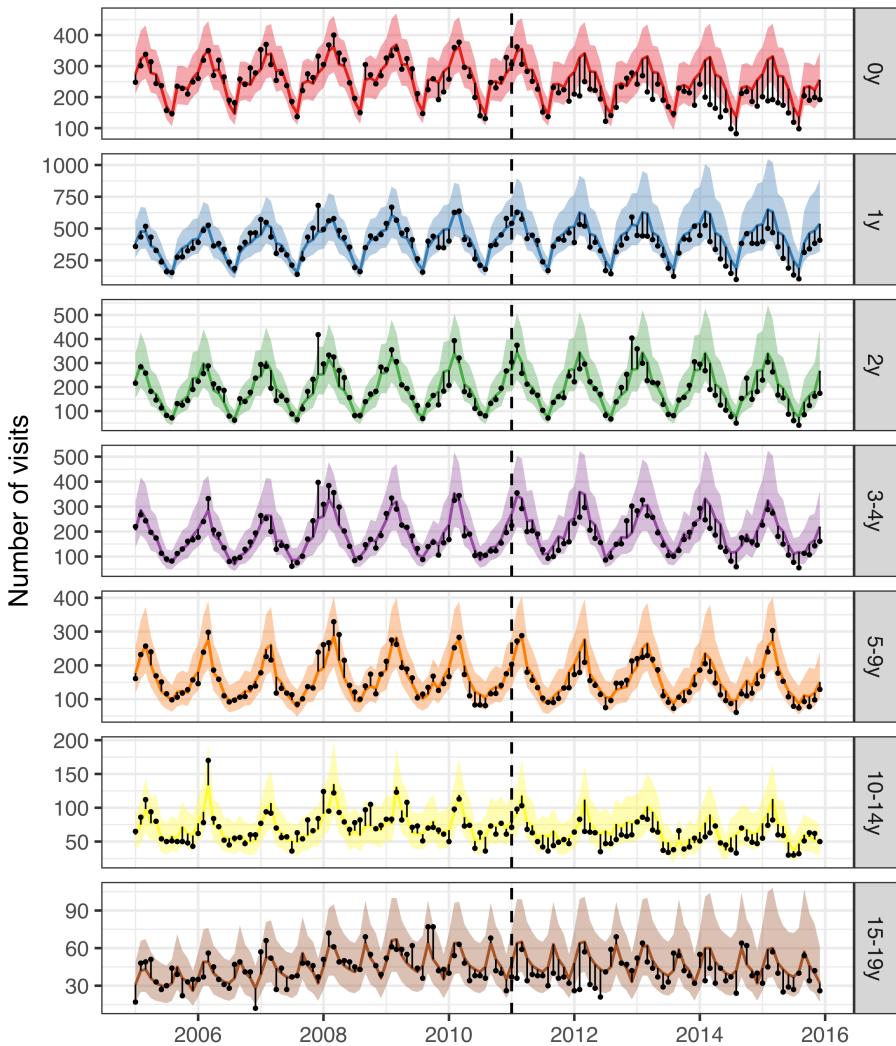


Figure 25. The observed and predicted number of AOM visits from 1 January 2005 to 31 December 2015 for each age-group. Observed visits are illustrated as black points, the posterior predicted visits are presented as lines and 95% credible intervals as a shaded area. The start of the vaccine period is delineated with a vertical black dotted line. The distance between the observed and predicted visits for each calendar-month is depicted with a thin black line. Assuming that the model is correct, and that no intervention had taken place, the black points would have an equal probability of occurring above and below the prediction line. Points below the lower bound of the shaded area would then represent observations that would have had less than a 2.5% probability of occurring. Given that the majority of points are located below the prediction line, and many located below the lower bound of the shaded area, the figure suggests that the vaccine resulted in fewer AOM visits. Note that the scale of the Y-axis differs between age-groups.

The rate ratios between the observed and predicted number of AOM cases are shown in Table 38. The 95% credible interval of the rate ratio was lower than one in all age-groups, indicating that there was a 97.5% or greater probability that the rate of AOM decreased due to the introduction of PHiD-CV10 in all age-groups. The decrease was largest among young children; 16% (12%-36%) in children younger than one year of age and 18% (5%-42%) in children one year of age. A 12-month rolling rate ratio between the observed and predicted number of AOM cases is presented in Panel A of Figure 26. Visually, the rate of AOM cases among children younger than one seems to begin to decline in January 2012, and cases among children one year of age seems to decline in July 2012.

Table 38 The rate ratio between observed and predicted number of primary care visits due acute otitis media and complications (AOM) during the post-vaccine period (2013-2015)

Table 38. The rate ratio between observed and predicted number of primary care visits due acute otitis media and complications (AOM) during the post-vaccine period (2013-2015), is presented with 95% credible intervals (95% CI) for the seven age-groups included in the study. The predicted cumulative number of prevented cases as of 1 December 2015 is also presented. A negative number indicates that there is a non-zero probability that the vaccine caused more AOM visits to occur. Direct and indirect savings are presented in constant 2015 USD.

Age-group	Rate ratio (95% CI)	Cumulative prevented (95% CI)	Direct savings (95% CI)	Indirect savings (95% CI)
0y	0.74 (0.64-0.88)	3,234 (1,008 to 5,195)	305,330\$ (90,933\$ to 514,848\$)	45,386\$ (11,143\$ to 84,654\$)
1y	0.72 (0.58-0.95)	5,802 (817 to 11,526)	530,468\$ (57,564\$ to 1,150,759\$)	74,298\$ (3,778\$ to 193,180\$)
2y	0.88 (0.66-0.98)	900 (-185 to 3,817)	92,117\$ (-52,649\$ to 407,227\$)	14,377\$ (-11,004\$ to 64,562\$)
3-4y	0.86 (0.69-0.97)	1,702 (21 to 3,576)	135,274\$ (-16,985\$ to 357,905\$)	23,880\$ (-4,324\$ to 62,811\$)

5-9y	0.88 (0.73-0.96)	979 (229 to 2,521)	134,548\$ (-38,612\$ to 430,729\$)	14,242\$ (-1,030\$ to 40,961\$)
10-14y	0.83 (0.75-0.92)	720 (411 to 1,086)	113,333\$ (4,669\$ to 285,816\$)	10,313\$ (-3,098\$ to 20,035\$)
15-19y	0.89 (0.56-0.98)	430 (210 to 1,689)	55,819\$ (-8,278\$ to 227,493\$)	6,169\$ (698\$ to 25,248\$)

The cumulative number of prevented AOM cases reflect both the rate of AOM cases in each age-group, and the consistency and magnitude of the vaccine effect. The cumulative prevented cases per age-group as of December 2015 are presented Table 38. The largest effects are seen in the youngest age-groups, who both had the highest baseline rates and experienced the largest relative declines following vaccine introduction. The cumulative number of prevented cases as a function of time during the post-vaccine period is shown in Panel B of Figure 26.

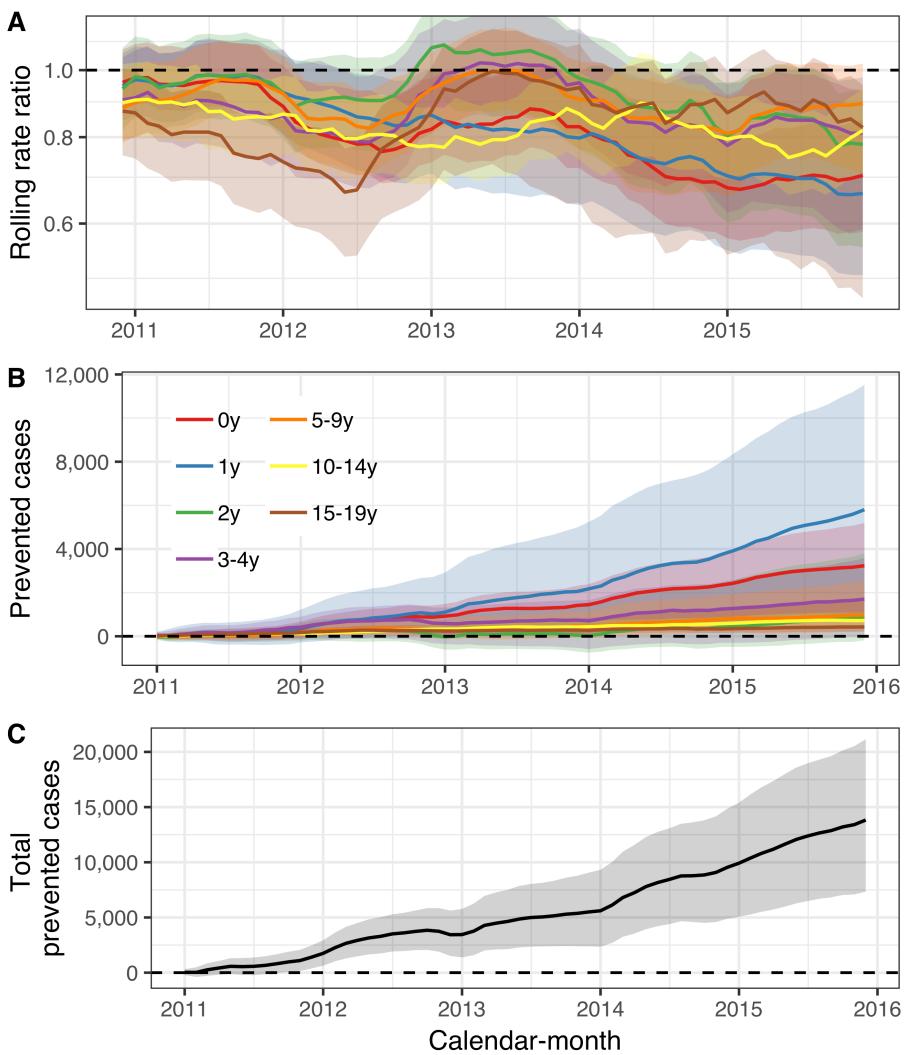


Figure 26. The impact of the 10-valent *Haemophilus influenzae* protein D pneumococcal conjugate vaccine (PHiD-CV10) on acute otitis media and complications (AOM) among children younger than 20 years of age is summarized. In Panel A, the estimated 12-month rolling rate ratio between observed and predicted AOM cases is shown per age-group, and the 95% credible intervals (CI) are illustrated as a shaded area. Panel B depicts the cumulative number of prevented AOM cases during the post-vaccine period (2011–2015) for each age-group, along with 95% CI. The total cumulative prevented AOM cases regardless of age-group is shown in Panel C.

The total cost of introducing PHiD-CV10 into the Icelandic pediatric vaccination program from 1 January 2011 to 31 December 2015 was 2,652,364\$ in constant 2015 USD. The vaccination resulted in 13,829 (7,337

to 21,114) prevented cases of AOM among children younger than 20 years of age by 1 December 2015 (Panel C of Figure 26). Given the observed distribution of costs associated with each AOM visit, the direct savings resulting from vaccine-prevented cases was 1,389,900\$ (95% credible interval 704,319\$ to 2,201,925\$). If the vaccine was assumed to have no other benefits other than preventing AOM, and only direct costs were considered, the incremental cost-effectiveness ratio was 91\$ (95% credible interval 21\$ to 259\$) per prevented AOM case from the health care perspective. The vaccine introduction prevented 10,911 days of work lost (95% credible interval 5,116 to 18,801), which translated to 194,152\$ (95% credible interval 78,200\$ to 364,155\$) in productivity gains. The ICER from the societal perspective was 76\$ (95% credible interval 6\$ to 244\$) per prevented AOM case, assuming the vaccine did not result in benefits in other manifestations of pneumococcal infections. When cost-savings due to reductions in hospital admissions for pneumonia and invasive pneumococcal disease were also included, the direct cost of the PHiD-CV10 introduction was -7,463,176\$ (95% credible intervals -16,159,551\$ to -582,135\$) as of 31 December 2015. From the health care perspective, the vaccination program was already cost-saving 7,463,176\$ in the first five years of the program. The corresponding ICER was -543\$ (95% credible interval -1,508\$ to -48\$) per prevented AOM case. When days of work lost due to hospitalized pneumonia and IPD cases were also included, the total cost of including PHiD-CV10 in the pediatric vaccination program was -8,164,894\$ (95% credible interval -17,197,959\$ to -1,004,553\$) as of 31 December 2015. The corresponding ICER was -594\$ (95% credible interval -1,597\$ to -76\$) per AOM case prevented.

#### **4.6.2 Population impact on pneumonia hospitalizations**

From 1 January 2005 to 31 December 2017, 13,373 hospitalizations for pneumonia were recorded. Monthly pneumonia hospitalizations displayed complex trends over the study period (Panel B of Figure 27). Pneumonia hospitalizations increased fairly rapidly during the pre-vaccine period among adults 40 years and older, and subsequently decreased at variable times in the post-vaccine period. Similarly, hospitalizations regardless of diagnosis increased among adults 20 years and older during the pre-vaccine period (Panel C of Figure 27).

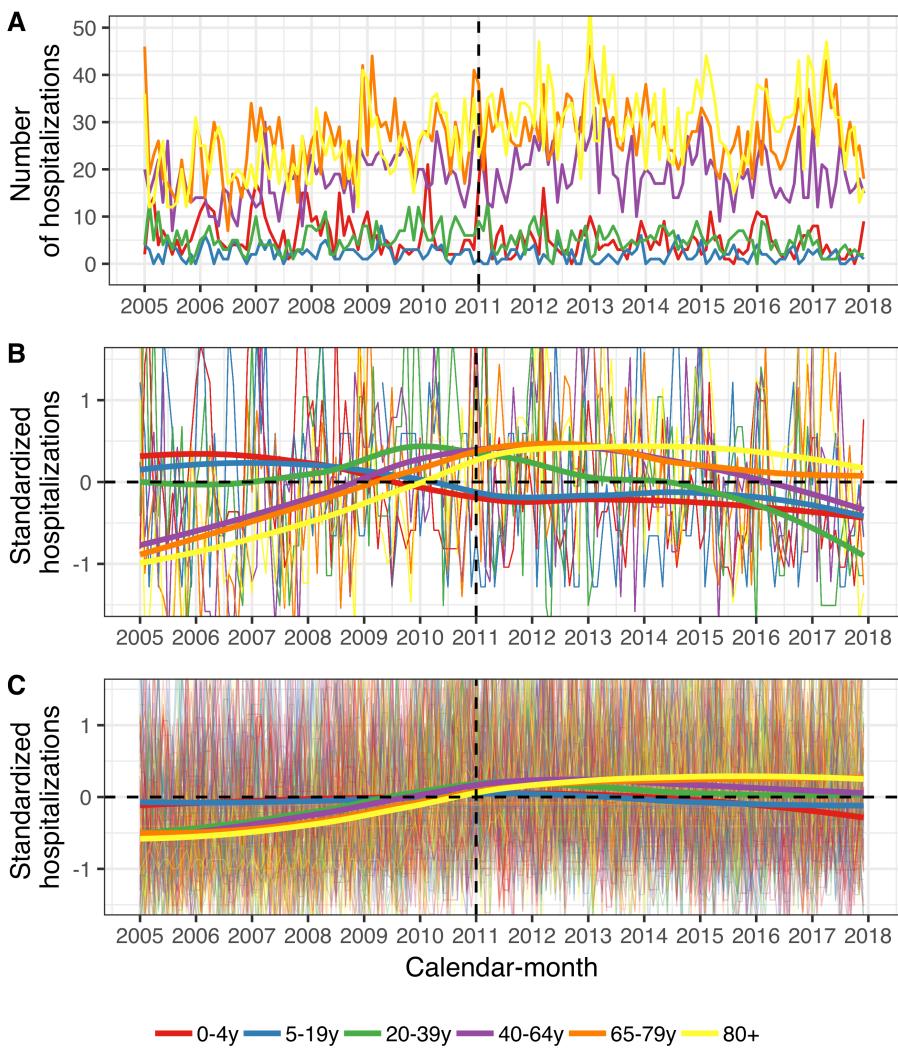


Figure 27. The monthly number of hospital admissions for pneumonia and hospitalizations regardless of diagnosis from 1 January 2005 to 31 December 2017. Panel A shows the monthly number of pneumonia hospitalizations. Panels B and C depict the standardized monthly number of pneumonia hospitalizations (Panel B) and all other hospitalizations (Panel C) per age-group. The Y-axis shows how many standard deviations from the mean the observed hospitalizations are by diagnosis and age-group. The horizontal dotted lines represent values that are zero standard deviations from the mean and the vertical dotted lines represent the start of the vaccine intervention. Locally estimated scatter-plot smoothing (LOESS) is used to produce an average trend.

The posterior predictions of the component models are shown in Figure 28. The predictions made by the ITS model without offset diverged from the

other models for all age-groups older than 20 years of age, and consistently predicted higher numbers of pneumonia hospitalizations.

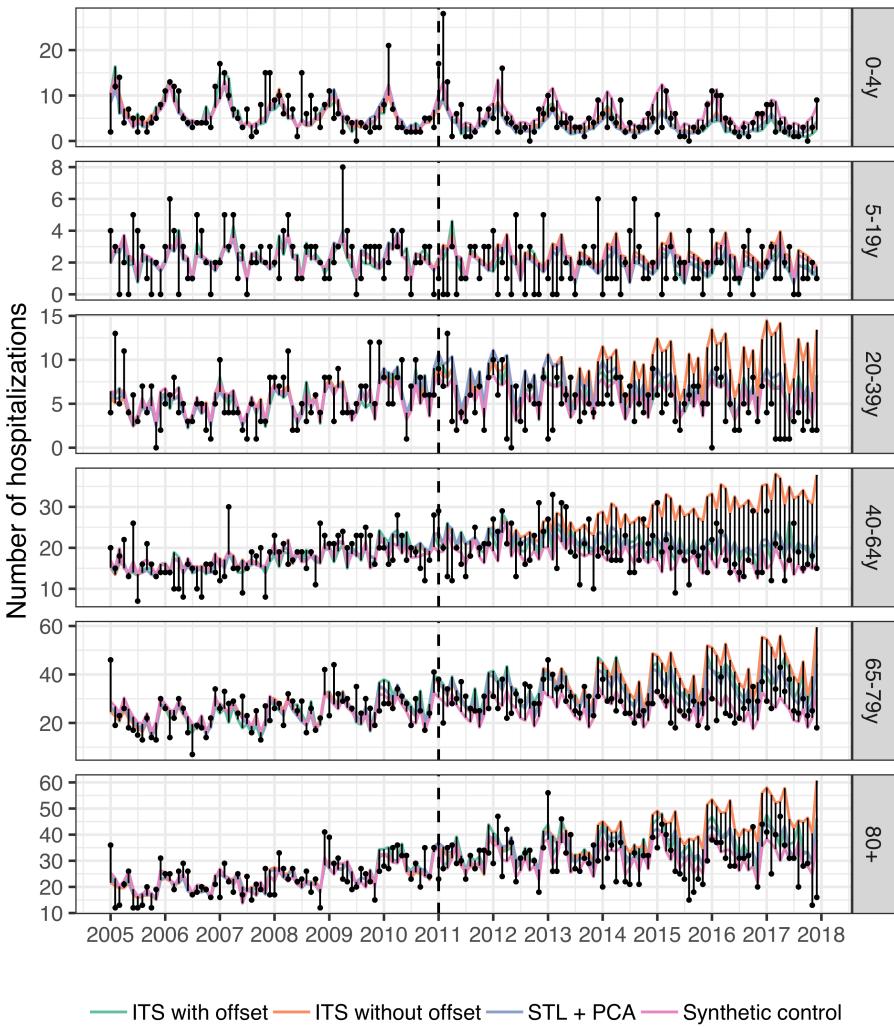


Figure 28. The observed and predicted number of pneumonia hospitalizations from 1 January 2005 to 31 December 2017 for each age-group. Observed cases are illustrated as black points and the predicted number of cases are drawn as lines for each of the component models. The start of the vaccine period is delineated with a vertical black dotted line. Each component model was fitted to the observed number of cases in the pre-vaccine period. They were then used to predict the number of cases that would have occurred in the post-vaccine period, had the vaccine not been introduced. The distance between the observed and predicted cases for each calendar-month is depicted with a thin black line. Longer distances suggest a larger discrepancy between observed and predicted cases. Note that the scale of the Y-axis differs between age-groups.

These component models were stacked using LOOCV to produce the final stacked model. The weights used to stack the component models are shown in Table 37. The predicted number of cases and 95% credible intervals are shown in Figure 29. During most of the post-vaccine period, the observed number of hospitalizations were equal to or below the prediction line among children zero to four years of age, and among adults 20 to 39, 65-79 and 80 years of age and older.

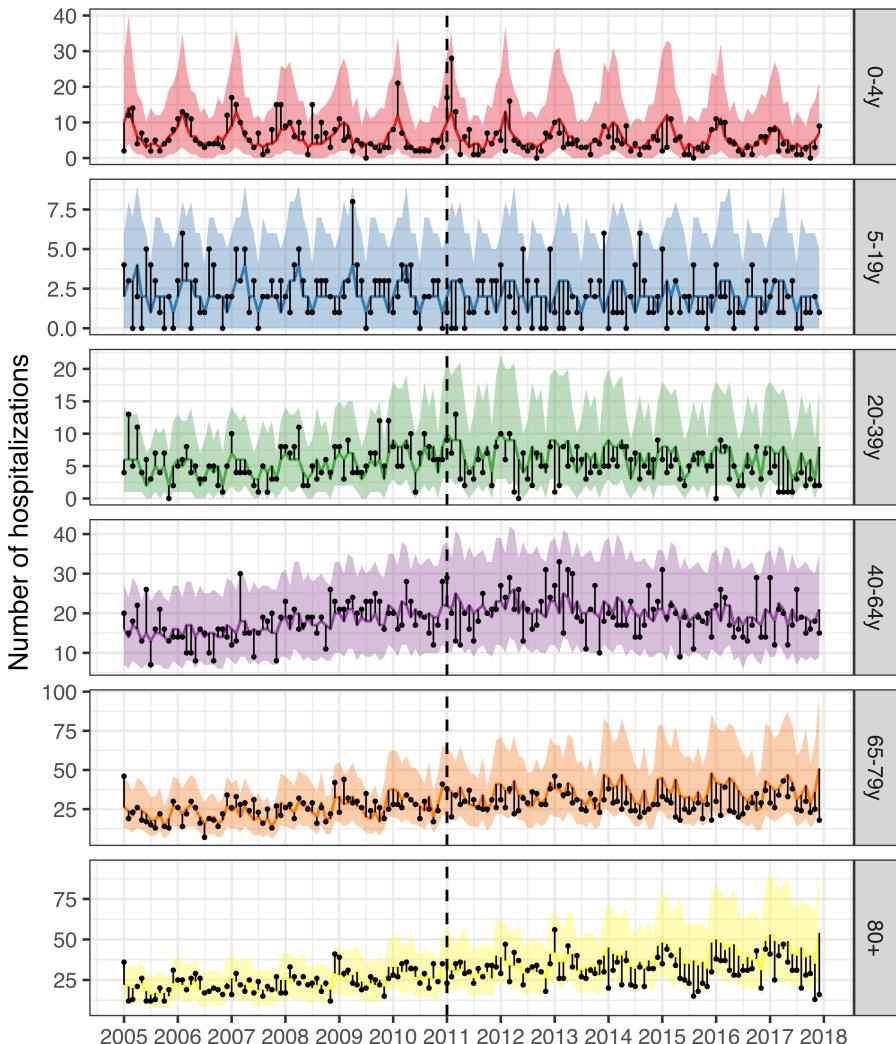


Figure 29. The observed and predicted number of pneumonia hospitalizations from 1 January 2005 to 31 December 2017 for each age-group. Observed cases are illustrated as black points. The predicted number of hospitalizations are presented as lines and 95% credible intervals as a shaded area. The start of the vaccine period is

delineated with a vertical black dotted line. The distance between the observed and predicted cases for each calendar-month is depicted with a thin black line. Assuming that the model is correct, and that no intervention had occurred, the black points would have an equal probability of appearing above and below the prediction line. Given that the majority of points are located below the prediction line, the figure suggests that the vaccine resulted in fewer pneumonia hospitalizations. Note that the scale of the Y-axis differs between age-groups.

The rate ratios between the observed and predicted number of pneumonia hospitalizations are shown in Table 39. Among children zero to four years of age, the posterior median of the rate ratio was 0.67, and the 2.5% credible limit was 0.51. This was consistent with a 2.5% probability that the rate ratio was lower than 0.51 and a 47.5% probability that the rate ratio laid between 0.51 and 0.67. Though the 97.5% credible limit was above the threshold value of one, there was a 94% probability that the rate ratio was lower than one, and a 90% probability that it was lower than 0.83. Similarly the posterior median of the rate ratio was 0.74 among children five to 19 years of age, and there was a 90% probability that the rate ratio was lower than one. Among adults 65 to 79 years of age, and 80 years of age and older, the posterior median of the rate ratio was 0.75 and 0.76 respectively, and both had a 97% probability of being lower than one.

A 12-month rolling rate ratio between the observed and predicted number pneumonia hospitalizations is presented in Panel A of Figure 30. Visually, the rate of pneumonia hospitalizations among children zero to four years of age seems to begin to decline in January 2012 (the first rolling 12-month period to include only post-vaccine months), and hospitalizations among adults 65 years of age and older seems to begin to decline in January 2014.

Table 39. The posterior median of the rate ratio between observed and predicted number pneumonia hospitalizations during the post-vaccine period (2013-2017) is presented with 95% credible intervals (95% CI) for the six age-groups included in the study. The predicted cumulative number of prevented cases as of 1 December 2017 is also presented. A negative number indicates that there is a non-zero probability that the vaccine caused more pneumonia hospitalizations to occur. Direct and indirect savings are presented in constant 2015 USD.

Age-group	Rate ratio (95% CI)	Cumulative prevented (95% CI)	Direct savings (95% CI)	Indirect savings (95% CI)
0-4y	0.67 (0.51-1.39)	142 (-115 to 307)	444,533\$ (-44,181\$ to 1,309,917\$)	52,535\$ (-59,043\$ to 136,715\$)

5-19y	0.74 (0.54-1.35)	52 (-27 to 113)	234,848\$ (-236,236\$ to 748,522\$)	20,472\$ (-18,876\$ to 61,481\$)
20-39y	0.68 (0.51-0.95)	182 (14 to 384)	968,662\$ (-203,048\$ to 2,567,059\$)	70,071\$ (-9,442\$ to 164,747\$)
40-64y	0.92 (0.79-1.22)	141 (-270 to 445)	933,290\$ (-2,748,49\$ to 4,848,557\$)	71,953\$ (-113,414\$ to 223,171\$)
65-79y	0.75 (0.55-1.02)	666 (-49 to 1,648)	5,476,585\$ (-910,021\$ to 15,590,280\$)	323,964\$ (-4,745\$ to 786,252\$)
80+	0.76 (0.56-1.02)	631 (-76 to 1,615)	4,664,256\$ (-817,266\$ to 13,013,699\$)	287,270\$ (-37,961\$ to 742,168\$)

The cumulative prevented pneumonia hospitalizations per age-group as of December 2017 are presented in Table 38. The largest effects were seen in adults 65 years of age and older, which reflects the baseline number of cases. The predicted cumulative number of prevented hospitalizations as a function of time during the post-vaccine period is shown in Panel B of Figure 30.

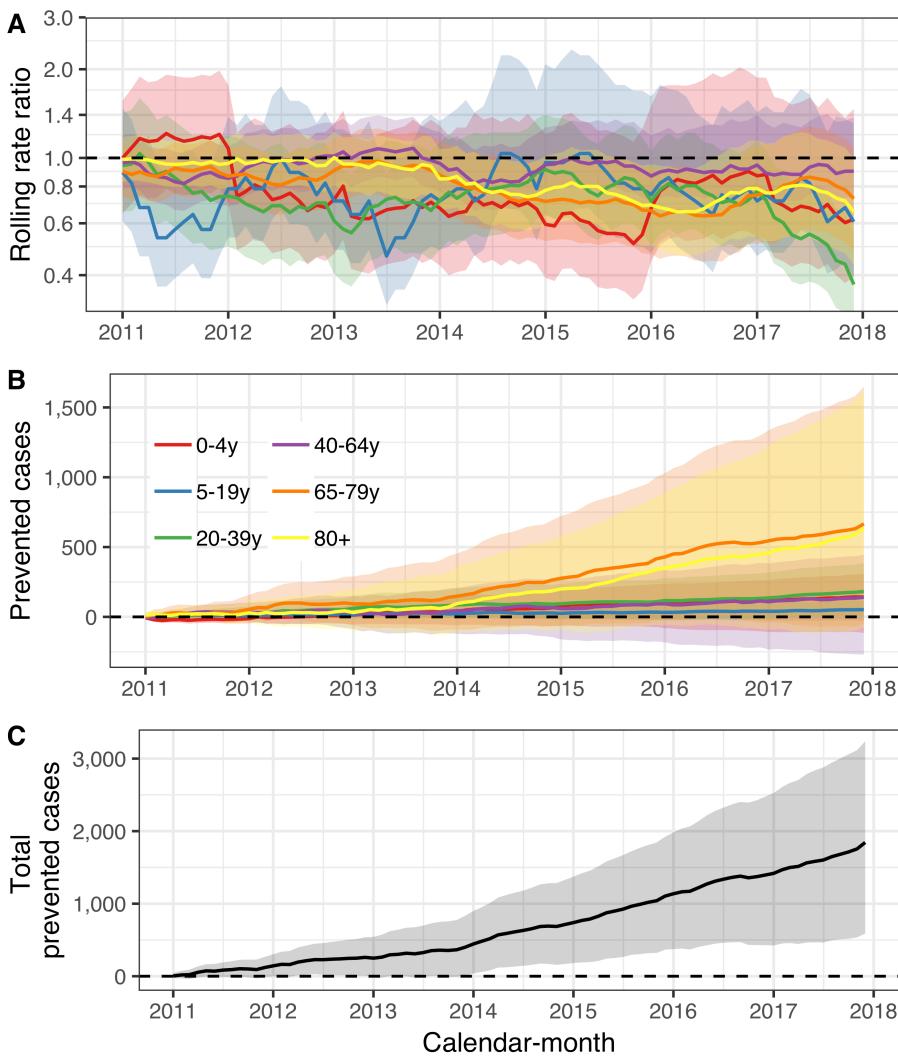


Figure 30. The population impact of the 10-valent *Haemophilus influenzae* protein D pneumococcal conjugate vaccine (PHiD-CV10) on pneumonia hospitalizations is summarized. In Panel A, the estimated 12-month rolling rate ratio between observed and predicted pneumonia hospitalizations is shown per age-group, and the 95% credible intervals (CI) are illustrated as a shaded area. Panel B depicts the cumulative number of prevented pneumonia hospitalizations during the post-vaccine period (2011-2017) for each age-group along with 95% CI. The total cumulative prevented pneumonia hospitalizations regardless of age-group is shown in Panel C.

The total cost of introducing PHiD-CV10 into the Icelandic pediatric vaccination program from 1 January 2011 to 31 December 2017 was 3,451,805\$ at constant 2015 USD. In total, the introduction of PHiD-CV10 resulted in 1,844 (589 to 3,239) prevented pneumonia hospitalizations in the

Icelandic population by 1 December 2017 (Panel C of Figure 30). Given the observed distribution of costs associated with each pneumonia hospitalization, the direct savings resulting from vaccine-prevented hospitalizations was 13,330,902\$ (95% credible interval 2,933,955\$ to 26,270,332\$), in constant 2015 USD. If the vaccine is assumed to have no other benefits than preventing pneumonia hospitalizations, and only the direct costs are considered, the ICER was -5,315\$ (95% credible interval -8,877\$ to 711\$) per prevented pneumonia hospitalization, indicating a net savings of 5,315\$ for each prevented hospitalization from the health care perspective. The vaccination program prevented 29,969 days of work lost (95% credible interval 9,964 to 52,900), which translated to 838,952\$ (95% credible interval 273,559\$ to 1,493,478\$) in productivity gains. From the societal perspective, the ICER was -5,794\$ (95% credible interval -9,275\$ to 24\$) per prevented pneumonia hospitalization, assuming no other vaccine benefit, which implies that the society gains 5,794\$ in constant 2015 USD for every pneumonia hospitalization prevented by investing in PHiD-CV10. If the vaccination program's effects on the other manifestations of pneumococcal disease were included, then the ICER was -5,640\$ (95% credible interval -10,336\$ to -1,032\$) in constant 2015 USD from the health care perspective as of 31 December 2015. Additionally including loss of work resulted in an ICER of -7,440\$ (95% credible interval -13,701\$ to -1,175\$).

#### **4.6.3 Population impact on hospital admissions for invasive pneumococcal disease**

From 1 January 2005 to 31 December 2016, 338 hospitalizations for culture confirmed invasive pneumococcal disease were recorded. Of those, 206 occurred before the introduction of PHiD-CV10 into the pediatric vaccination program in Iceland. Hospital admissions due to vaccine-type IPD were 175, of which 138 occurred prior to vaccine introduction. Only two vaccine-type IPD hospitalizations of children zero to four years of age were recorded in the post-vaccine period. Both cases were unvaccinated, and both occurred in 2011. This is compared to 32 hospital admissions of the same age-group in the pre-vaccine period. The number of vaccine-type IPD cases were not sufficiently many to perform a time series analysis.

Standardized hospitalizations for IPD decreased among children zero to four years of age, while standardized hospital admissions regardless of cause did not decrease to the same extent (Panels B and C of Figure 31). Discrepancies between hospital admissions for IPD and all-cause hospitalizations were also noted in the other age-groups. Hospitalizations for

IPD among individuals five to 64 years of age decreased while all-cause hospitalizations remained stable. While hospital admissions for IPD among adults 65 years of age and older did not change visibly, the standardized all-cause hospitalizations increased, suggesting a relative decline in IPD admissions.

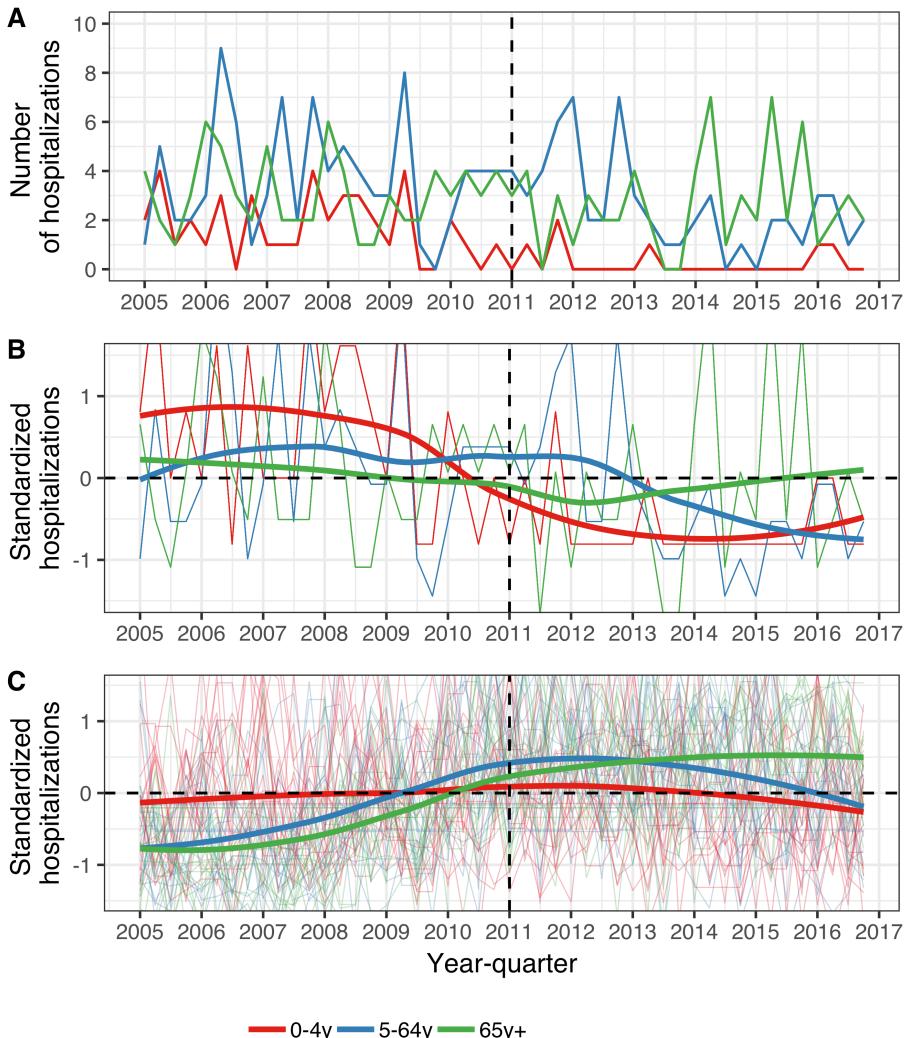


Figure 31. The number of hospitalizations per year-quarter from 1 January 2005 to 31 December 2016. The population is divided into three age-groups, listed in the figure legend. Panel A shows the absolute quarterly number of hospital admissions due to invasive pneumococcal disease (IPD) regardless of serotype. Panels B and C, depict the standardized quarterly number of IPD hospitalizations (Panel B) and all-cause hospitalizations (Panel C) per age-group. The Y-axis represents the number of standard deviations from the mean hospitalizations for each quarter and each age-

group. The horizontal dotted lines represent values that are zero standard deviations from the mean and the vertical dotted lines represent the start of the vaccine intervention. Locally estimated scatter-plot smoothing (LOESS) is used to produce an average trend. Panels B and C have been magnified to emphasize the interpretation of the trend line. Panels B and C show that standardized hospitalizations for IPD decreased in all age-groups, relative to the standardized hospitalizations regardless of cause.

The posterior predictions of the component models are shown in Figure 32. Both the ITS models consistently predicted fewer IPD cases among children zero to four years of age in the post-vaccine period, compared to the STL + PCA and synthetic control models.

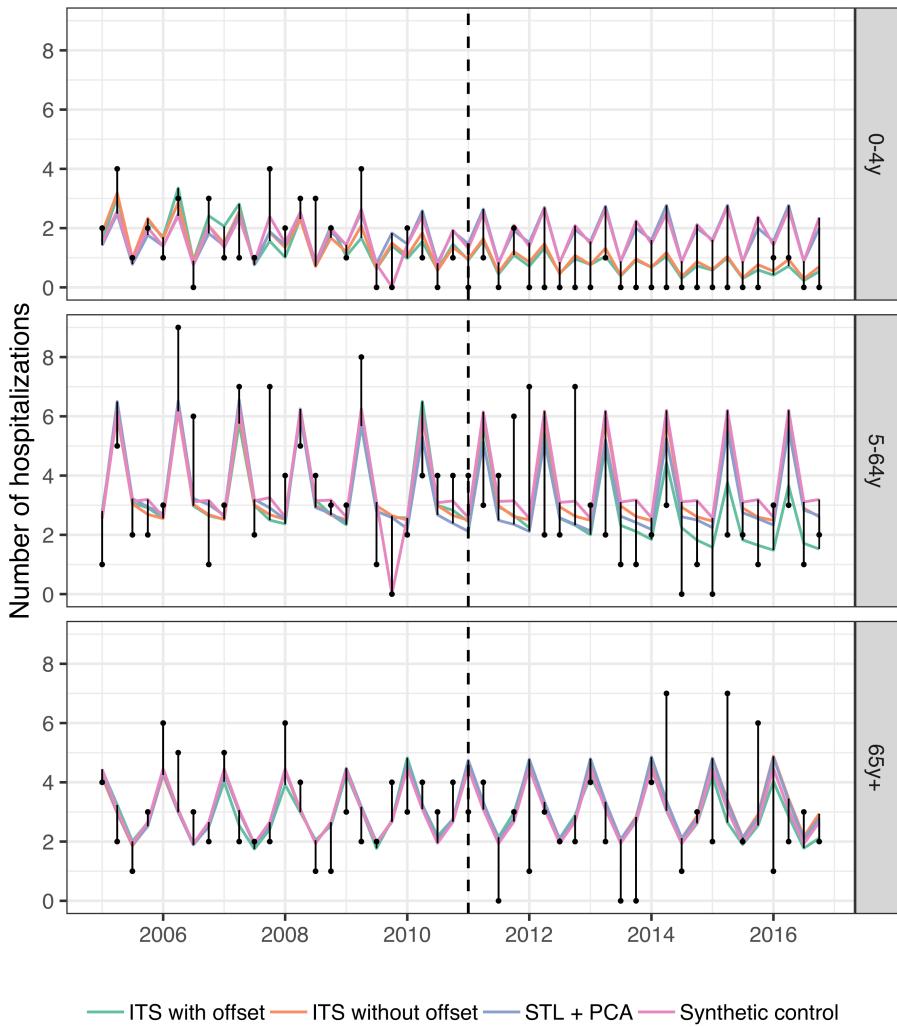


Figure 32. The observed and predicted number of IPD hospitalizations from 1 January 2005 to 31 December 2016 for each age-group. Observed cases are illustrated as black points and the predicted number of cases are drawn as lines for each of the component models. The start of the vaccine period is delineated with a vertical black dotted line. Each component model was fitted to the observed number of cases in the pre-vaccine period. They were then used to predict the number of cases that would have occurred in the post-vaccine period, had the vaccine not been introduced. The distance between the observed and predicted cases for each year-quarter is depicted with a thin black line. Longer distances suggest a larger discrepancy between observed and predicted cases.

The stacked model for children zero to four years of age was comprised of the synthetic control model weighted at 0.001 and ITS with offset weighted at

0.999. For individuals five to 64 years of age, and adults 65 years of age and older, the LOOCV procedure assigned full weight to the synthetic control model, excluding contributions from the other three.

The posterior prediction of IPD hospitalizations and 95% credible intervals are shown in Figure 33. Among children zero to four years of age, observed IPD hospitalizations were equal to or fewer than the predicted hospitalizations in all but two quarters. Similarly, observed hospitalizations among individuals five to 64 years of age were fewer than predicted more often than expected. Both suggest that the vaccine prevented cases from occurring.

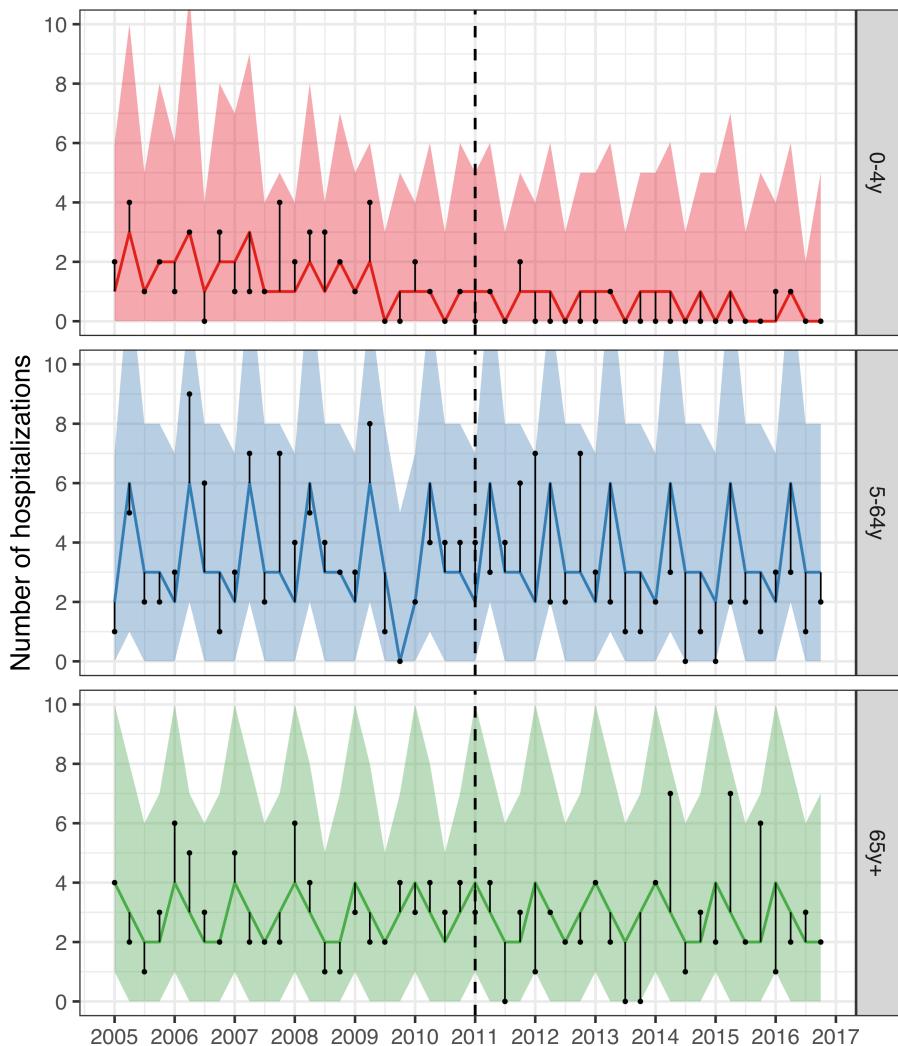


Figure 33. The observed and predicted number of IPD hospitalizations from 1 January 2005 to 31 December 2016 for each age-group. Observed cases are illustrated as black points, and the predicted number of cases are presented as lines with 95% credible intervals as a shaded area. The start of the vaccine period is delineated with a vertical black dotted line. The distance between the observed and predicted cases for each year-quarter is depicted with a thin black line. Assuming that the model is correct, and no intervention had taken place, the black points would have an equal probability of occurring above and below the prediction line. Given that the majority of points are located below the prediction line, the figure suggests that the vaccine resulted in fewer IPD hospitalizations.

The rate ratios between the observed and predicted number of IPD hospitalizations in the post-vaccine period are shown in Table 40. The

posterior median of the rate ratio for children younger than five years of age was 0.27, corresponding to a 50% probability that the vaccine impact was greater than or equal to 73%. The 95% credible intervals of the rate ratio were wide, reflecting the uncertainty due to the few number of IPD hospitalizations. However, 90% of the MCMC draws of the rate ratio were below 0.75 and 93% were under the threshold value of one. The 95% credible interval of the rate ratio among individuals five to 64 years of age was lower than one, indicating a 97.5% or greater probability that the rate of IPD hospitalization decreased in this age-group following the introduction of PHiD-CV10.

The 12-month rolling rate ratio is presented in Panel A of Figure 34. The rolling rate ratio for children zero to four years of age was unstable due to numerical issues with both the numerator and the denominator. In some 12-month periods, no IPD hospitalizations were observed and the resulting rate ratio was zero regardless of the denominator. In other periods, 2.5% or more of the MCMC draws predicted zero IPD hospitalizations, which resulted in a 95% credible intervals of the rate ratio that extended towards infinity. These issues do not change the overall interpretation of the prediction line presented in Panel A of Figure 34 or the rate ratios presented in 38.

Table 40. The rate ratio between observed and predicted number of hospital admissions for invasive pneumococcal disease (IPD) during the post-vaccine period (2013-2016) is presented along with 95% credible intervals (95% CI) for the three age-groups. The predicted cumulative number of prevented cases as of 1 December 2016 is also presented. A negative number indicates that there is a non-zero probability that the vaccine caused more IPD hospitalizations to occur. Direct and indirect savings are presented in 2015 USD.

Age-group	Rate ratio (95% CI)	Cumulative prevented (95% CI)	Direct savings (95% CI)	Indirect savings (95% CI)
0-4y	0.27 (0.05-3.00)	14 (-2 to 67)	227,087\$ (71,363\$ to 618,919\$)	16,882\$ (6,893\$ to 38,718\$)
5-64y	0.44 (0.31-0.68)	29 (1 to 65)	321,424\$ (-455,573\$ to 1,649,171\$)	12,983\$ (-3,606\$ to 33,498\$)
65y+	0.94 (0.62-1.53)	10 (-16 to 45)	73,395\$ (-256,856\$ to 516,864\$)	4,340\$ (-10,903\$ to 23,543\$)

The cumulative prevented IPD hospitalizations per age-group as of December 2016 are presented Table 39, and are shown as a function of time in Panel B of Figure 34. The posterior median of the cumulative prevented cases increases from the beginning of the post-vaccine period among children zero to four years of age.

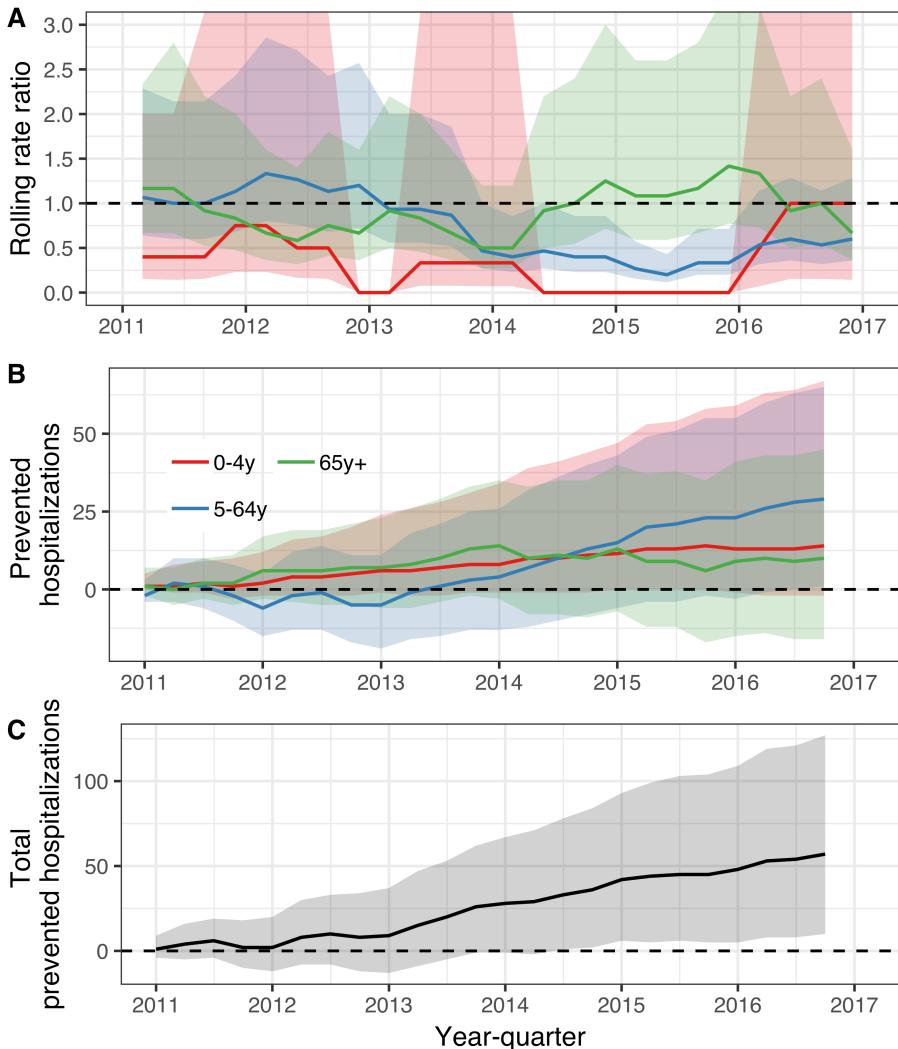


Figure 34. The population impact of the 10-valent *Haemophilus influenzae* protein D pneumococcal conjugate vaccine (PHiD-CV10) on hospital admissions for invasive pneumococcal disease is summarized. In Panel A, the estimated 12-month rolling rate ratio between the observed and predicted number of IPD hospitalizations in the post-vaccine period (2011-2016) is shown per age-group. Panel B depicts the cumulative number of prevented IPD hospitalizations during the post-vaccine period (2011-2015)

for each age-group along with 95% credible intervals. The total cumulative prevented IPD hospitalizations regardless of age-group is shown in Panel C.

In total, by December 2016, the introduction of PHiD-CV10 prevented 57 (10 to 127) cases of IPD serious enough to warrant hospital admission (Panel C of Figure 34). The total cost of introducing PHiD-CV10 into the Icelandic pediatric vaccination program from 1 January 2011 to 31 December 2016 was 3,097,861\$, in constant 2015 USD. Given the observed distribution of costs associated with each IPD hospitalization, the direct savings resulting from vaccine-prevented hospitalizations of IPD was 673,008\$ (95% credible intervals -189,654\$ to 2,081,594\$). If the vaccine was assumed to have no other benefits than preventing IPD hospitalizations, and only the direct costs are considered, the ICER was 30,134\$ (95% credible interval 8,488\$ to 80,375\$) per prevented IPD hospitalization. The vaccine introduction prevented 1,280 days of work lost (444 to 2,410) due to IPD, which translated to 35,280\$ (95% credible intervals 9,437\$ to 70,609\$) in productivity gains. If the vaccine was assumed to have no other benefits than preventing IPD hospitalizations, the ICER from the societal perspective was 30,134\$ (95% credible intervals 8,487\$ to 80,375\$) per prevented IPD hospitalization. When cost-savings due to reductions in AOM visits or hospital admissions for pneumonia were also included, the ICER was -119,992\$ (95% credible interval -387,183\$ to -9,542\$) per prevented IPD hospitalization from the health care perspective. When days of work lost were also considered, the ICER was -130,791\$ (95% credible interval -416,004\$ to -15,860\$) per prevented IPD hospitalization.

## **5 Discussion**

### **5.1 Main findings**

- The pediatric pneumococcal vaccination program that was implemented in Iceland in 2011 achieved excellent coverage. Over 97% of all children in the first six vaccine eligible birth-cohorts received two or more doses of PHiD-CV10 before 24 months of age.
- An impact of PHiD-CV10 introduction was detected on several different facets of otitis media incidence. Pediatric primary care visits due to acute otitis media decreased by 21% and emergency department visits to Children's Hospital Iceland decreased by 12-21%. Hospital-based treatment of otitis media with parenteral ceftriaxone decreased by 42%.
- All-cause outpatient antimicrobial prescriptions decreased by 8% among children younger than three years of age following the introduction of PHiD-CV10. The incidence of AOM-associated antimicrobial prescriptions decreased even further, 21%.
- The incidence of tympanostomy tube placements did not decrease following the introduction of PHiD-CV10, despite a measurable impact on otitis media visits to primary care and pediatric emergency departments and antimicrobial prescriptions. Approximately one-third of all Icelandic children undergo at least one tympanostomy tube procedure before five years of age.
- Pediatric hospital admissions for pneumonia declined by 20% following PHiD-CV10 introduction. Pneumonia hospitalizations were also shown to have decreased among Icelanders 20-39 years of age, implying a strong herd-effect among adults likely to be the parents of young children.
- Invasive pneumococcal disease requiring hospitalization decreased by 93% among vaccine-eligible children younger than three years of age. No vaccine-type invasive disease was diagnosed among the vaccinated cohorts.
- The pediatric pneumococcal vaccination program in Iceland was cost-effective. During the first five years of the program, PHiD-CV10 resulted in a net-savings of 7,463,176 \$ when only considering averted costs of prevented cases. When work-loss was also considered, the estimated net-savings increased to 8,164,894 \$.

### **5.2 Data collection and sources (Papers I-VI)**

The data used for the papers in this thesis were collected from several population-based registries. Their quality and scope are extensive.

Three of the registries are maintained by the Icelandic Directorate of Health. Firstly, data on every administered dose of pneumococcal conjugate vaccine were obtained from the National Vaccine Registry. The NVR receives data directly from the electronic health record system. Secondly, information regarding every outpatient antimicrobial prescription was extracted from the National Drug Prescription Registry, which receives electronic data directly from Icelandic pharmacies when each prescription is filled. Compliance is required by law. Finally, primary care visits for respiratory infections were extracted from the Primary Care Registry, which contains records on all visits to primary care physicians in Iceland.

Information on emergency department visits and hospital admissions for respiratory infections were obtained from Landspítali University Hospital's patient registry. Landspítali University Hospital is the sole tertiary hospital in Iceland, and includes Iceland's only pediatric hospital. It accounts for 91% of all hospital beds in the country, provides primary and secondary care for 65% of the Icelandic population, and provides tertiary care for the whole population. The patient registry is maintained by administrative staff at Landspítali University Hospital.

Landspítali's patient registry included a detailed breakdown of costs for each visit and hospitalization. Cost was broken down into categories which included wages of physicians, nurses, and other support staff, as well costs of medications and diagnostic testing. The costs incurred by each department involved in the patient's care was tabulated. These data were used in the cost-effectiveness analysis.

The reimbursement database of Icelandic Health Insurance provided data on all outpatient otolaryngological procedures. While the reimbursement database is not directly connected to electronic medical records, there is still strong reason to believe that the database is accurate and contains information on all outpatient procedures. Health care in Iceland is a single-payer system with the government guaranteeing equal access for all permanent residents through a single national health insurance, which is funded by taxation. Health care providers are either salaried governmental employees or independent practitioners who work within a framework agreement with Icelandic Health Insurance, and are reimbursed on a per case basis. It is unreasonable to assume that any Icelandic resident would routinely forgo their national health insurance and opt to pay the full cost out-of-pocket. Likewise, independent practitioners have a strong incentive to

seek compensation for their labor. The data available from the reimbursement database therefore reflect the total number of procedures.

Immigration and emigration data on children younger than five years of age were provided by Statistics Iceland. The data augmented birth-cohort analyses, allowing longitudinal time-to-event analyses to be performed. Children who immigrated to Iceland after birth could be excluded and the follow-up time of children who emigrated could be censored at the time of emigration.

Data from each registry were transferred directly to the Directorate of Health where the data was anonymized. Each record was associated with a unique study identification number that was created from the individual's national identification number by staff at the Directorate of Health. Because each Icelandic citizen receives one and only one national identification number over the course of their lifetime, this allowed the data from the various registries to be reliably linked. Unique individuals could be tracked between the different registries but could not be identified.

The linkage between several large population-based registries overcame a common limitation of epidemiological data. Registries record information about an event that occurred, e.g. an antimicrobial prescription, a primary care visit or a hospital admission. Because of this, they generally lack information about those individuals who did not experience the event. Epidemiological studies are therefore often forced to either restrict their scope to individuals who experienced one or more events, or infer the number of individuals who did not experience an event. Individual-level data on those who did not experience the event is missing. By linking large concurrent population-based registries, we were able overcome this common constraint by accurately identifying unique individuals who were alive and living in Iceland during the evaluated period.

The data underlying this study were observational in nature, and their quality was enhanced by several factors. The breadth of the data was extensive. The study contains individual-level information on 375,383 Icelandic citizens over a 13 year period from 2005-2017. Six years of data were collected prior to the introduction of PHiD-CV10 into the pediatric vaccination program, which allowed for an analysis of secular trends in the pre-vaccine period. Similarly, the study included five to seven years of post-vaccine data, providing an opportunity to evaluate the immediate and delayed effect of vaccine introduction. According to Statistics Iceland, the aggregate number of Icelandic citizens was 293,577 on 1 January 2005, and was

338,349 on 1 January 2017 – which strongly suggests that our data contains individual-level information on all Icelandic citizens with few exceptions.

Though the data were extracted from the registries after events occurred, they were collected prospectively, and retain the properties of prospectively collected data. Retrospective observational studies identify a population of individuals who have experienced a certain event, and then determine what risk-factors they had prior to experiencing the event. A prospective study identifies a population of interest and follows them over time to ascertain whether they experience a certain event. Prospective data can produce estimates of relative and absolute risk, and relative and absolute rates.

Electronic medical records were consistent during the entire study period. Not only were all medical records in Iceland stored electronically, but the same software, *Saga*, was used by all health care providers and institutions throughout the study period. Likewise, the International Classification of Diseases, 10th revision (ICD-10), was the only diagnostic coding system in use in Iceland during the study period. Furthermore, all medical procedures were coded with the NOMESCO Classification of Surgical Procedures (NCSP), and drugs were classified using the Anatomical-Therapeutic-Chemical (ATC) classification system of the World Health Organization. Continuity between data systems enhanced the quality of results.

Our data included the date of birth, date of death, as well as data on immigration and emigration of Icelandic children. Through linkage of the registries, individual-level information of those who did not experience an event became available, and accurate time-based at-risk denominators could be constructed. This allowed the study data to be analyzed using survival methods, and repeated events within the same individual taken into account.

Individual-level information was available for each pneumococcal vaccine dose that was administered in Iceland. Unlike prior studies, which were forced to infer the proportion of individuals who were vaccinated using aggregate sales data, we were able to directly check if a person had been vaccinated. We were also able to confirm that few children had been vaccinated in Iceland before the introduction of PHiD-CV10 into the Icelandic pediatric vaccination program. Among birth-cohorts 2005-2009, the proportion of children who received two or more doses of a pneumococcal conjugate vaccine before two years of age was below 3%. Of the non-vaccine eligible birth-cohorts, only the 2010 birth-cohort saw an increase in PCV uptake, especially among children born in the latter half of 2010. This is likely due to heightened awareness among parents because of the impending

introduction of the vaccine. In some sense the result is that an unplanned catch-up occurred, with close to 40% of children born in the latter half of 2010 receiving two or more doses of a pneumococcal conjugate vaccine, before two years of age.

### **5.3 Epidemiology and management of otitis media in Iceland and the impact of PHiD-CV10 introduction (Papers I, II, III, V and VI)**

Following the introduction of PHiD-CV10, changes were noted in several facets of otitis media epidemiology and its management. These changes were summarized in papers I, II, III, V and VI.

#### **5.3.1 Epidemiology of acute otitis media in Iceland (Papers II and V)**

Acute otitis media is often a benign temporary infection that will in many cases resolve without intervention (Thornton et al. 2011). The epidemiology of AOM is influenced by the distribution of risk-factors in the population, and by cultural factors that influence the propensity of parents to consult physicians (Blank et al. 2014; Fortanier et al. 2015). The epidemiology of AOM is therefore often highly variable between countries, as documented in Table 1. Despite this, AOM is the most common reason for physician visit among children, a fact which has been frequently documented in multiple countries (Arguedas et al. 2010; Marchisio et al. 2012; Monasta et al. 2012).

The epidemiology of acute otitis media visits to primary care was described in paper II. During the 11 year study period from 2005 to 2015, the overall incidence of AOM episodes among children zero to three years of age was 42 per 100 person-years. Prior to the introduction of PCV into the Icelandic pediatric vaccination program, 59% of children had visited a primary care physician one or more times by their third birthday and each child had experienced 1.6 episodes on average. The impact of PHiD-CV10 is discussed in Chapter 5.3.2. There were large variations in the incidence rate between both gender and age. The incidence was consistently higher in males than females. This gender difference has been documented in several different prospective studies of AOM epidemiology (Baraibar 1997; Macintyre et al. 2010; Paradise et al. 1997). However, the mechanism by which gender affects AOM incidence is unknown. The incidence of AOM increases from birth and peaks among children eight to 15 months of age. The abrupt peak at eight to 15 months of age and subsequent decrease may be hypothesized to be a function of two competing processes; the exposure of the child to

pathogens due to daycare center attendance and the development of immunity to common pathogens (Hoog et al. 2014).

The incidence of AOM is highly variable between countries. Generally, the rate of AOM among European children ranges from 15 to 40 episodes per 100 person-years (Adam and Fehnle 2008; Esposito et al. 2007; Gisselsson-Solen 2017; Gribben et al. 2012; Lau et al. 2015; Liese et al. 2014; Marchisio et al. 2012; Todberg et al. 2014; Usonis et al. 2016), while the rate among children in the United States ranges from 95 to 200 episodes per 100 person-years (De Wals et al. 2009; Grijalva et al. 2006; Grijalva, Nuorti, and Griffin 2009; Poehling 2004; Zhou et al. 2008). With an incidence rate of 42 episodes per 100 person-years, the rate of AOM in Iceland seems to be higher than published estimates from most other European countries, but lower than published estimates from the United States. To our knowledge, only one previous study has reported the cumulative incidence of AOM in a modern cohort, demonstrating a 60% cumulative incidence by seven years of age (Todberg et al. 2014). Additionally, two studies from the twentieth century showed an 83% cumulative incidence by three years of age and 66% by two years of age (Bjarnason, Friðriksson, and Benediktsson 1991; Teele, Klein, and Rosner 1989). We observed a cumulative incidence of 59% by four years of age. Though not directly comparable to the other studies, this seems to suggest that the cumulative incidence is higher than a concurrent modern cohort in Denmark, but lower than historical cumulative rates. These differences between countries may be due to a multitude of different factors – some related to the distribution of risk factors in the population, others due to cultural differences that influence the ascertainment rate of AOM cases. Finally, some of the variation is likely due to design of the studies reporting the epidemiology of AOM.

Of studies that have examined the epidemiology of AOM, ours is the only longitudinal population-based study. We followed 11 birth-cohorts from birth until four years of age and accounted for censoring due to emigration. We accounted for follow-up visits for the same episode of AOM by excluding visits within 30 days of the index visit. Most of the other studies obtained aggregated AOM visits within a portion of the population and divided this with the aggregated number of children (De Wals et al. 2009; Gisselsson-Solen 2017; Grijalva et al. 2006; Grijalva, Nuorti, and Griffin 2009; Lau et al. 2015; Poehling 2004; Zhou et al. 2008). By using aggregated AOM visits as the numerator, they cannot exclude re-visits for the same AOM episode, which artificially inflates the incidence of AOM. The remaining studies followed individual children, but were not population-based and ascertained cases at

variable time-points after six months of age (Adam and Fehnle 2008; Esposito et al. 2007; Gribben et al. 2012; Liese et al. 2014; Usonis et al. 2016).

The pathophysiology and microbiology of AOM are discussed in chapter 1.1.1. The most common bacterial causes of otitis media are non-typeable *Haemophilus influenzae* (NTHi), *Streptococcus pneumoniae* and *Moraxella catarrhalis* (Bluestone, Stephenson, and Martin 1992; Casey and Pichichero 2004; Casey, Adlowitz, and Pichichero 2009; Ngo et al. 2016; Pumarola et al. 2013). The relative contribution of these three pathogens is remarkably stable between countries and over time (Ngo et al. 2016). This is likely a consequence of how common they are in the nasopharyngeal flora of children. A systematic review of studies from 1970-2014 which reported the etiology of otitis media, found that *Streptococcus pneumoniae* caused 30% of acute otitis media in Europe (Ngo et al. 2016). Our research group has shown that prior to PHiD-CV10 introduction in Iceland, the proportion of otitis media with tympanic perforation that was caused by pneumococcus was 20% (Quirk et al. 2018). This is similar to other countries (Ngo et al. 2016). The contribution of other pathogens has not yet been evaluated in Iceland. There does not seem to be strong evidence to suggest that the distribution of pathogens is different in Iceland than in other high-income countries, and thus other factors likely explain the difference in epidemiology.

The propensity to seek medical care may be influenced by several cultural and socio-economic factors. Access and cost of health care may influence whether parents consult a physician and may result in measurable changes in incidence between countries (Fortanier et al. 2015; Hadley 2003; Smolderen 2010). In Iceland, all permanent residents are provided health insurance by the government and there is excellent access to urgent care. Children are provided health care free of charge. The employment rate of Icelandic adults 20-64 years of age is 91% and 84% for males and females respectively, which means that Iceland has the highest employment rate in Europe (Eurostat 2018). These factors may push parents to seek early care for otitis media and would result in higher estimates of AOM incidence that would be closer to the true incidence in the population. This may also lead to overdiagnosis and overtreatment. Employment can however not explain the higher incidence reported in studies from the United States, as the employment rate is considerably lower, with only 76% and 66% of working age men and women employed (OECD 2019).

Iceland is ranked third in formal daycare attendance by The Organization for Economic Co-operation and Development (OECD), with up to 60% of children under three years of age attending a daycare center for 38 hours per week or longer. This is compared to the OECD average of 35% attendance for 30 hours ("Enrolment in childcare and pre-schools" 2013). Both daycare attendance and the number of hours per week are known risk factors for acute otitis media (Ramakrishnan, Sparks, and Berryhill 2007) These factors could result in a higher incidence of AOM in Iceland relative to other countries and may explain some the observed difference between Iceland and other European countries. However, this does not explain why studies conducted in the United States consistently show higher incidence rates of AOM than Icelandic estimates. The rate of early daycare attendance in the United States is half that of Iceland, and below the average of OECD countries ("Enrolment in childcare and pre-schools" 2013).

Taken together, our population-based study of all primary care visits for acute otitis media over an 11 year period is likely to have ascertained a large proportion of true cases. To our knowledge, we report the only population-based follow-up of AOM incidence from birth to four years of age. The study reminds us that ratio statistics do not tell the whole story. Longitudinal studies are important to capture other perspectives on disease incidence. We report a 59% cumulative incidence of AOM by four years of age. The mean number of AOM episodes per child was 1.6, and 42% of children experienced two or more episodes. This better represents the burden of disease than ratio statistics such as 42 AOM episodes per 100 person-years, though such statistics also have their place.

### **5.3.2 Impact on primary care visits for otitis media (Papers II and VI)**

Pneumococcal conjugate vaccines have been shown to reduce the incidence of acute otitis media in both randomized and observational trials. Eight randomized control trials examined the effect of PCV on AOM, demonstrating large decreases in pneumococcal AOM and moderate decreases in all-cause AOM (Black et al. 2000; Dagan et al. 2001; Eskola et al. 2001; Fireman et al. 2003; Kilpi et al. 2003; O'Brien et al. 2008; A. Palmu et al. 2015; Prymula et al. 2006; Tregnaghi et al. 2014; Vesikari et al. 2016). Two systematic reviews of observational studies examining the impact of PCV on the incidence of AOM identified nine studies, of which three accounted for pre-vaccine trends in AOM incidence and only one was population-based (Ben-Shimol et al. 2014; Grijalva et al. 2006; Grijalva, Nuorti, and Griffin 2009; Poehling 2004;

Poehling et al. 2007; Lau et al. 2015; Magnus et al. 2012; Marom et al. 2014; Singleton et al. 2009). We report the results of two separate population-based studies estimating the impact of PHiD-CV10 on otitis media visits in primary care. The studies used different methods which complemented each other with regards to underlying assumptions, weaknesses and strengths.

Paper II reported the results of a population-based, individual-level birth-cohort study. The crude incidence rate of AOM visits to primary care decreased from 45 to 40 per 100 person-years among children zero to three years of age following vaccine introduction. Accounting for repeated episodes, the estimated impact of PHiD-CV10 was 21%. Of the previously identified observational studies, only three included individual-level data (Ben-Shimol et al. 2014; Magnus et al. 2012; Poehling et al. 2007).

Ben-Shimol et al. (2014) reported a prospective population-based study of middle-ear fluid cultures from a single-center in Israel following sequential PCV7 and PCV13 introduction. The study found a 96% and 85% impact on vaccine-type pneumococcal AOM, and a 60% reduction in all-cause AOM, but only obtained data on cases serious enough to be referred to the center for tympanocentesis. The propensity of physicians to refer otitis media cases for tympanocentesis was not evaluated. Changes in referral patterns may have potentially confounded the observed reduction in all-cause AOM, but would not be expected to confound vaccine-type AOM.

Magnus et al. (2012) utilized prospectively collected data from the Norwegian Mother and Child Cohort Study to estimate the rate of AOM before and after the introduction of PCV7. Mothers were recruited from 39 of 50 maternity units in Norway and data was collected by questionnaires at six, 18 and 36 months of age. The questionnaire only asked the mother whether their child had experienced AOM between 12-18 months of age, and 18-36 months of age, and did not specify the frequency or whether a physician was consulted. The study reported a 14% and 8% vaccine impact on the parent-reported prevalence of one or more AOM episodes in children 12-18 months of age and 18-36 months of age respectively.

Poehling et al. (2007) examined the hazard ratio of frequent otitis media between birth-cohorts enrolled in an state-insurance program before and after the introduction of PCV7. Four birth-cohorts 1998-2001 were included and followed to five years of age; the first two (1998-1999) were considered unvaccinated and the latter two (2000-2001) were considered vaccinated. Impact was reported by comparing the 1998 birth-cohort to the 2000 birth-cohort, and by this metric the vaccine impact on frequent AOM was 17%-

28%. However, the largest decrease was seen between the birth-cohorts 1998 and 1999, with almost no difference seen between the 1999 and 2000 birth-cohorts and no explanation or theory was provided in the discussion chapter.

Paper II adds to the current literature by providing robust population-based, individual-level observational evidence of PHiD-CV10 impact on all-cause AOM. As an outcome-measure, physician diagnosed AOM in primary care is more applicable for policy decisions than is the parent-reported prevalence of AOM, frequent AOM and otitis media requiring tympanocentesis. To our knowledge, this was the first study to directly account for repeated episodes within the same individual and employ survival methods that accounted for confounding by age and censoring. This allowed us to examine vaccine impact from perspectives that are not normally available to observational studies. In addition to impact on traditional ratio measures, we were able to show that the proportion of children who had never experienced an AOM episode increased from 40% in the vaccine non-eligible cohorts to 43% among vaccine eligible children. The vaccine impact was shown to independently protect against a child's first and second episode, but in the subset of children who had already experienced two or more episodes of AOM, the vaccine was not shown to decrease the hazard of experiencing an additional episode. Longitudinal data on each child allowed us to calculate the mean number of AOM episodes at 36 months of age, and show that this had decreased from 1.61 among vaccine non-eligible children to 1.31 among vaccine eligible children.

By utilizing population-based data, our study avoided selection bias, which may have confounded the results of previous studies. Selection bias is possible in Ben-Shimol et al. (2014) if providers deferentially referred children for middle-ear sampling based on their vaccination status and may have occurred in Magnus et al. (2012) if the propensity of mothers to continue submitting questionnaires at 18 and 36 months was modified by the frequency of AOM in the child. Though Poehling et al. (2007) used a similar registry approach as our study, their population included only children of insured families. Despite these weaknesses, it should be noted the results of the above studies were congruent with a positive impact of PCV, which our study also confirmed.

Our study was strengthened by its long observational period which included six vaccine non-eligible birth-cohorts and five vaccine eligible birth-cohorts. Though paper II did not directly adjust for observed trends, the long

pre-vaccine period provided context to the large and abrupt decrease in the hazard of AOM noted between the last vaccine non-eligible cohort (2010) and the first vaccine eligible cohort (2011). Such context would have been useful in interpreting Poehling et al. (2007), were the largest decreases in frequent AOM was noted between the first and second unvaccinated cohorts. Despite the strengths of paper II, the lack of adjustment for secular trends remained an important weakness.

Paper VI estimated the impact of PHiD-CV10 on physician diagnosed AOM in primary care taking into account pre-vaccine trends using a time series methodology. Four different methods were independently used to predict vaccine impact, which were then stacked by maximizing the predictive performance of the final model. This approach optimally accounts for secular trends and allows estimation of herd-effect in older children who were not vaccine eligible in the post-vaccine period. Using this method, the vaccine impact was 26% among children younger than one year of age, 28% among one year olds, 12% among two year olds and 14% among children three to four years of age.

Of the identified observational studies evaluating the impact of PCV on otitis media, only three have attempted to correct for secular trends (Grijalva et al. 2006; Lau et al. 2015; Marom et al. 2014). Grijalva et al. (2006) reported the rate of otitis media visits in the United States before and after PCV7 introduction. They estimated that PCV7 was associated with a 20% decline in the rates of otitis media among children younger than two years of age. The rate ratio of otitis media visits between children younger than two years of age and children three to six years of age were compared visually between the pre-vaccine period, transition year and a single post-vaccine year. The ratio of rate ratios was then calculated between the pre-vaccine period and post-vaccine year, and used as a measurement of impact. The largest decreases in the rate of otitis media visits among children younger than two years of age were observed before the introduction of PCV7, yet no explicit adjustment was made for pre-vaccine trends.

Lau et al. (2015) used an interrupted time series approach to estimate the sequential impact of PCV7 and PCV13 on otitis media in general practice, and reported a 21.8% reduction in the rate of otitis media visits in children younger than 10 years of age. The pre- and post-vaccine periods were appropriately long and the study was well conducted, though the methods only allowed adjusting for linear trends, which may both over- and underestimate underlying trends (Bernal,

Cummins, and Gasparrini 2016; Kontopantelis et al. 2015). The data was extracted from the IMS Disease Analyser; a longitudinal electronic health care database maintained by a for-profit health care information company. The database receives information from general practitioners who applied to participate and received compensation for manually contributing deidentified data. This process may select for general practitioners who are more self-reflective and adhere more strictly to evidence based medicine than do the general population of physicians.

Finally, Marom et al. (2014) used data on privately insured children younger than seven years of age in the United States from 2001-2011 to estimate the rate of otitis media visits before and after the introduction of PCV13 in 2010, using a linear time series analysis. They employed a similar approach as Grijalva et al. (2006), calculating rate ratios of otitis media visits between children younger than two years of age and children three to six years of age. They reported a stable rate ratio of 1.38 in the pre-vaccine period, which decreased to 1.01 in 2011 following the introduction of PCV13. Marom et al. (2014) did not report a single estimate of PCV13 impact. However, if they had calculated impact similarly to Grijalva et al. (2006), the estimated impact would have been 27%.

Paper VI adds to the current literature by providing population-based data on the impact of systematic vaccination with PHiD-CV10 on acute otitis media visits to primary care that is adequately adjusted for secular trends. Our study compliments previous studies examining the impact of PCV on otitis media visits and improves on them in several ways.

We used four models to adjust for secular trends, each with their own strengths and weaknesses. Two simple time series models were constructed, with and without a population offset. These two models were comparable to those that have been used by previous studies to adjust for secular trends, but improved upon them by allowing trends to be non-linear (Lau et al. 2015; Marom et al. 2014). Two additional models were included which incorporated data on primary care visits for other causes. A synthetic control framework was used, in which the relationship between otitis media visits and visits for other indications was estimated in the pre-vaccine period, and this relationship was used to predict the number of otitis media visits that would have occurred in the post-vaccine period, had PHiD-CV10 not been introduced (Bruhn et al. 2017; Shioda et al. 2018). The models were then optimally combined to maximize the predictive performance of the final stacked model. Using these methods we were able to adjust for secular

trends and were not forced to assume that trends were linear and predictive uncertainty was minimized by incorporating data on observed visits to primary care for other indications.

By using population-based data, the possibility of selection bias was eliminated. Grijalva et al. (2006) and Marom et al. (2014) only include privately insured children and Lau et al. (2015) only includes visits to a self-selected subset of general practitioners. This selection has unknown significance with regards to the outcome being measured. It should however be noted, that while our study improves upon previous studies in many ways, the results of our study is congruent, demonstrating a large impact of PCV on otitis media.

In any vaccine ecology study, one must be careful when interpreting the results, as confounding may have contributed to over- or underestimation of the estimated vaccine impact. The impact of PHiD-CV10 on AOM in Iceland is quantified using two different methods that complement one another. Paper II provided individual-level evidence of vaccine effect, and the longitudinal data allowed us to report unique measurements of impact, such as cumulative incidence and the mean number of episodes as a function of age. However, the methods did not allow adjustment for trend. Paper VI used several different methods to capture pre-vaccine trends and predict how many AOM episodes were prevented by PHiD-CV10 introduction. Thus, we were able to adjust for trend to a degree that has not previously been published in impact studies evaluating AOM. Despite the different methodologies, the results of paper II and paper VI are consistent. The point-estimate in both papers are similar and the diminishing vaccine impact seen in older children with the time series methodology is mirrored in the incidence rate ratios between the vaccine eligible and vaccine non-eligible birth-cohorts displayed in Figure 9.

Taken together, we believe that the impact of PHiD-CV10 on AOM has been demonstrated beyond a reasonable doubt. Using population-based data, we have removed the confounding threat of selection bias. The individual-level cohort study provided robust evidence with well delineated exposures and time at-risk, and the time series analysis adjusted the estimated impact for secular trends. This is an important addition to the current literature on PCV, as otitis media is the most common childhood infection that leads to physician visits and antimicrobial prescriptions (Arguedas et al. 2010; Marchisio et al. 2012; Monasta et al. 2012).

### **5.3.3 Impact on pediatric emergency department visits for acute otitis media (Paper I)**

Acute otitis media is generally a benign self-limiting condition, and cases that require treatment usually respond well to oral antimicrobials (Ahmed, Shapiro, and Bhattacharyya 2014). However, AOM can progress to recurrent or chronic infection and require more invasive treatment (Cullen, Hall, and Golosinskiy 2009; Vlastarakos et al. 2007). One example of this is mastoiditis – a rare but serious complication of AOM that invariably requires hospital admission and administration of intravenous antimicrobials (Finnbogadóttir et al. 2009; Groth et al. 2011).

Paper I examined the impact of PHiD-CV10 introduction on the incidence of AOM visits to the emergency department of Children's Hospital Iceland. Following vaccine introduction, the incidence decreased significantly from 4.7 visits per 100 person-years in the pre-vaccine period to 4.1 visits per 100 person-years in the post-vaccine period. The estimated vaccine impact was 12%. The study employed a simple pre/post design, and was not able to adjust for secular trends due to the nature of the study data. However, we did show that the AOM visits decreased despite an increase in all-cause visits. The design was similar to most previously published observational studies of PCV on AOM (Vojtek, Nordgren, and Hoet 2017).

Emergency department visits for AOM are likely to represent a subset of more serious cases than those that present to primary care centers. It is therefore important to establish impact in both settings, as they represent different aspects of AOM epidemiology and burden of disease. This observed decrease in the incidence of emergency department visits probably reflects the effect of PHiD-CV10 to reduce not only AOM in general but also more serious manifestations of AOM. A robust time series approach with synthetic controls is warranted to further investigate the impact of PHiD-CV10 on pediatric emergency department visits for acute otitis media, as was done in paper VI for primary care.

### **5.3.4 Impact on outpatient antimicrobial prescriptions for otitis media (Paper III)**

Antimicrobial consumption is directly linked to antimicrobial resistance on both the individual and population levels (Blommaert et al. 2014; Bruyndonckx et al. 2015; Costelloe et al. 2010; Goossens et al. 2005). Otitis media is responsible for the majority of antimicrobial prescriptions in children, and thus contributes significantly to antimicrobial resistance (Austin, Kristinsson, and Anderson 1999; Grijalva, Nuorti, and Griffin 2009).

The impact of the introduction of PHiD-CV10 on outpatient antimicrobial prescriptions for AOM was explored in Paper III, using population-based registries. Data were obtained from the Icelandic National Drug Prescription Registry which included all filled outpatient antimicrobial prescriptions during a thirteen year period from 2005 to 2017. These were linked to visits to primary care physicians for AOM which were extracted from the Primary Care Registry. The vaccine impact on AOM associated antimicrobial prescriptions was 22%, adjusting for the number of previous antimicrobial prescriptions. The impact was 6% on all antimicrobial prescriptions regardless of indication.

Several randomized controlled trials have estimated the vaccine efficacy of PCV on outpatient antimicrobial consumption, with results ranging from 5% to 15% (Dagan et al. 2001; Fireman et al. 2003; Palmu et al. 2014). Dagan et al. (2001) specifically examined efficacy against otitis media associated antimicrobial days, and reported 20% vaccine efficacy. Our results are within reasonable bounds of these findings.

Though blinded randomized controlled trials do provide robust estimates of vaccine efficacy, they do so under artificial conditions. Parents and physicians may behave differently knowing that their actions are being observed and quantified by researchers, and this may reduce the incidence of inappropriate prescribing. In that respect, observational studies provide additional information by demonstrating whether vaccine impact can still be observed in true clinical settings. To our knowledge, only one study has previously assessed the impact of PCV on otitis media associated antimicrobial prescriptions, which demonstrated a 20% vaccine impact (Lau et al. 2015). Two other observational studies on outpatient antimicrobial prescriptions demonstrated an association between PCV introduction and a decline in prescriptions (Gefenaite et al. 2014; Howitz et al. 2017).

To our knowledge, our study was the first to estimate the individual-level impact of pneumococcal vaccination on antimicrobial prescriptions and directly account for repeated prescriptions within the same child. This allowed a much sharper delineation between vaccinated and unvaccinated children. When data are aggregated and analyzed based on calendar-time, the period from the introduction of the vaccine until the majority of children under observation are vaccinated will span several years. During that time, other secular trends exert their confounding effects on the outcome, and the start of the post-vaccination period is not well defined. Contrast this with our cohort study where children in the 2010 cohort, who were not vaccine eligible, were directly compared to the vaccine eligible children in the 2011 cohort. Though

the children in the 2010 birth-cohort were one year older on average, the two cohorts experienced the same viral epidemics, were treated by the same physicians and interacted with each other daily in daycare centers.

By including six non-eligible cohorts and five eligible cohorts, we were able to adequately visualize secular trends. A decreasing trend in the hazard of AOM associated antimicrobial prescriptions was noted in the vaccine non-eligible cohorts, such that the hazard was significantly higher in the 2007 compared to the 2010 birth-cohort. Though this may change the point-estimate, the large, abrupt and significant hazard decrease between the 2011 and 2010 birth-cohorts strongly suggests a true vaccine impact.

Our study adds to the current literature by providing population-based, individual-level data on the impact of PHiD-CV10 on AOM-associated antimicrobial prescriptions. Assessing the impact of vaccination on antimicrobial prescriptions is an important outcome measure as it captures a subset of outpatient AOM cases that is serious enough to warrant treatment. It encompasses both a physician's diagnosis of AOM, and the decision to treat. Our data suggest that PCV and other vaccines may be an important tool in the fight against antimicrobial resistance, by decreasing antimicrobial prescriptions among children.

### **5.3.5 Evidence of herd-effect of PHiD-CV10 on the incidence of otitis media in the unvaccinated population (Papers II and VI)**

Vaccination decreases the susceptibility of vaccinated individuals to become infected, and later decreases the risk of passing the pathogen to others. Therefore, there is strong reason to believe that introducing PHiD-CV10 into the population could confer indirect protection against pneumococcal disease to non-vaccinated members of the population. In vaccine studies, this indirect effect is termed herd-effect, and has been convincingly demonstrated for invasive pneumococcal disease following introduction of pneumococcal conjugate vaccines (Tsaban and Ben-Shimol 2017). There is a paucity of published literature demonstrating herd-effect for acute otitis media following pneumococcal conjugate vaccine introduction (Jennifer D Loo et al. 2014).

In paper II, a large decrease in the incidence of AOM was found among children younger than four months of age. The incidence rate ratio between children in the vaccine eligible cohorts compared to children in the vaccine non-eligible cohorts was 0.60 (0.51-0.69), which translates to a 40% vaccine impact in this age-group. Children three to four months of age may have

already received the first dose of PHiD-CV10, but will not yet have received any direct benefit (Nicholls, Leach, and Morris 2016). Thus, the data strongly supports existence of a herd-effect for AOM, and that vaccinating children at three, five and 12 months of age with PHiD-CV10 confers protection to children too young to be themselves directly protected. One previous study reported fewer positive pneumococcal cultures from samples taken from the middle ear of children younger than four months of age, following the sequential introduction of PCV7 and PCV13 in Israel, suggesting a possible herd-effect (Ben-Shimol et al. 2016). Though population-based, their case ascertainment was dependent on referral for tympanocentesis from primary care physicians, and it is unclear from the publication whether the proportion of cases referred changed following vaccination. Any such change could introduce an artificial decrease following vaccination. Unlike Ben-Shimol et al. (2016), we included all cases of AOM presenting to primary care physicians. Our study is the first to suggest herd-effect against all-cause physician-diagnosed AOM among children too young to receive the vaccination.

In paper VI, a time series methodology with synthetic controls was applied to ascertain the PHiD-CV10 impact on otitis media visits in primary care. The study period was 2005-2015, during which none of the vaccine eligible children had reached five years of age. The vaccine impact was estimated separately in children younger than one, one, two, three to four, five to nine, 10-14 and 15-19 years of age. The estimated vaccine impact was 12%, 17% and 11% in children five to nine, 10-14 and 15-19 years of age respectively. For these estimates the 95% credible intervals did not cross the ratio value of one, which translates to a 97.5% or higher probability that the impact was larger than or equal to 1%. The result is consistent with a strong herd-effect of PHiD-CV10 against otitis media in unvaccinated older children. We are unaware of any previously published study which confirms the existence of herd-effect against AOM in older children and believe our results to be unique. Because the data regarding visits to primary care for other indications were aggregated for children zero to 11 months of age, we were unable to test for herd-effect among children younger than four months of age using the time series methodology. Visual examination of Figure 9 does not suggest a decreasing pre-vaccine trend in AOM episodes among children younger than four months of age, and therefore the result would be expected to be the same.

We believe the results of paper II and paper VI to be an important addition to the current literature regarding herd-effect of pneumococcal vaccination. AOM is associated with a large individual and societal burden of disease

(Greenberg et al. 2003; Monasta et al. 2012). Our studies show that countries that introduce PCV into their national immunization programs can and should expect a decrease in AOM episodes among age-groups not covered by the vaccination program, in addition to a larger direct decrease among vaccinated children. This provides further evidence of PCV benefit and should inform future cost-utility analyses.

### **5.3.6 Impact on acute otitis media with treatment failure (Paper I)**

There is a paucity of published studies that examine the impact of pneumococcal conjugate vaccines on acute otitis media with treatment failure. Treatment failure is generally defined as the persistence of symptoms despite antimicrobial treatment, though precise definitions vary (Casey and Pichichero 2004). There is evidence to suggest that treatment failure occurs more commonly in AOM caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* than in AOM caused by other pathogens (Casey and Pichichero 2004; Pichichero et al. 2008). Otitis media with treatment failure represents an important subset of cases that is associated with a higher burden of disease.

In paper I, the impact of PHiD-CV10 on the incidence of AOM episodes treated with parenteral ceftriaxone at Children's Hospital Iceland was examined. Data regarding the use of ceftriaxone and visits for AOM were extracted from Children's Hospital Iceland's patient registry for the period from 2008 to 2015. When ceftriaxone is used in the treatment of AOM at Children's Hospital Iceland, it is done exclusively in cases of treatment failure, difficult recurrent infections or in culture-proven antimicrobial-resistant pneumococcus. The study demonstrated a statistically significant 52% impact of PHiD-CV10 on ceftriaxone treated AOM episodes among children younger than four years of age.

To our knowledge, this is the first study to show a significant decrease in AOM with treatment failure following PCV introduction. Because AOM with treatment failure is not objectively defined in the literature, a proxy measurement such as ceftriaxone use is needed. Parenteral antimicrobial use is avoided unless absolutely necessary and is not administered at primary care clinics. It is therefore an appropriate and clinically relevant proxy measurement for the worst cases of otitis media with treatment failure.

We do however acknowledge that we are not currently in possession of data that proves that a trial of oral antimicrobials was attempted prior to

initiation of parenteral ceftriaxone. It is an assumption that is grounded in established clinical norms of pediatric medicine. Unlike the other study data upon which this thesis is based, the data used in paper I was not linkable to population registries, which precludes formal evaluation of this assumption.

Several evaluations were performed to examine other possible explanations for the observed decrease. To exclude the possibility that the observed reduction was due to a decrease in AOM cases, the analysis was repeated using the number of AOM visits to Children's Hospital Iceland as the rate denominator, if this statistic were used, the estimated vaccine impact would have been 42%. No changes were observed in ceftriaxone usage among older children, and among children younger than four, ceftriaxone use for indications other than AOM and pneumonia did not change significantly, with an estimated incidence rate ratio 0.96 (95% CI: 0.87-1.06). Though not statistically significant, the observed rate ratio does not prove an absence of effect. The result is consistent with as much as a 13% decrease in the incidence of ceftriaxone treatment for indications other than AOM and pneumonia. This may be partly explained by the inclusion of indications other than AOM and pneumonia that are possibly related to PCV, such as unspecified fever, cough and sepsis.

No changes in institutional guidelines regarding the use of ceftriaxone or treatment of severe AOM occurred during the study period. When the totality of evidence is considered, our study suggests a true independent association between the introduction of PHiD-CV10 into the Icelandic pediatric vaccination program, and the observed decrease in AOM treated with parenteral ceftriaxone. Clinical experience tells us that this may be considered a proxy for AOM with treatment failure.

### **5.3.7 Impact of PHiD-CV10 on tympanostomy tube placements (Paper IV)**

Tympanostomy tube placements are the most common pediatric surgical procedure requiring general anesthesia (Black 1984; Cullen, Hall, and Golosinskiy 2009). The most common indications for the procedure are recurrent acute otitis media and otitis media with effusion, however evidence of benefit is inconsistent (Venekamp et al. 2018; Browning et al. 2010). In paper IV, we report the impact of PHiD-CV10 introduction into the Icelandic pediatric vaccination program on tympanostomy tube placements. This population-based study obtained data on tympanostomy procedures from the reimbursement database of Icelandic Health Insurance and Landspitali University Hospital's patient registry. The estimated impact was -5% (95%CI -

15% to 4%), indicating a non-significant increase in the hazard of tympanostomy tube placement following vaccine introduction.

The results are neither congruent with the results of other studies included in this thesis, or previously published randomized controlled trials and observational studies. Papers II and III demonstrated a clinically meaningful decrease in primary care visits, and antimicrobial prescriptions for AOM and all-cause outpatient antimicrobial prescriptions. The results of randomized controlled trials are summarized in Table 3. Black et al. (2000) demonstrated a 20% efficacy of PCV7 for tympanostomy tube procedures, and four other randomized studies showed a non-significant preventative effect (Eskola et al. 2001; O'Brien et al. 2008; Prymula et al. 2006; A. Palmu et al. 2015). Two observational studies have examined the effect of PCV on tympanostomy tube procedures; one was conducted in the United States reported reductions in the risk of tympanostomy procedures following the introduction of PCV7, but did not consider the possibility of secular trends (Poehling et al. 2007). The other was conducted in Australia carefully evaluated secular trends and other confounders, and reported a 23% reduction in the rate of procedures associated with the introduction of PCV7 (Jardine et al. 2009).

We report an incidence of 106 procedures per 1,000 person-years in children zero to five years of age, and a cumulative incidence of 32% by six years of age. This represents both the highest incidence rate and cumulative incidence of tympanostomy procedures that has been published to date (Table 2). We demonstrated that among children who underwent tympanostomy tube placement, the proportion of children who had never visited a primary care physician or filled an antimicrobial prescription prior to the procedure was higher in the vaccine eligible cohorts. The study design does not allow us to estimate the cause of this unexpected increase. We know of no plausible biological explanation for the consistently high proportion of Icelandic children who undergo invasive treatment for a benign self-limiting disease. Our study provides evidence that children who underwent tympanostomy placement after the introduction of PHiD-CV10 had fewer AOM associated visits and had filled fewer antimicrobial prescriptions at the time of surgery. We believe that the high incidence and cumulative incidence of tympanostomy tube procedures both before and after systematic pneumococcal vaccination in Iceland warrants further study and scrutiny by both researchers and the Icelandic Directorate of Health.

## **5.4 Impact of PHiD-CV10 on hospital admissions for respiratory infections and invasive pneumococcal disease (Papers V and VI)**

Infections that require close monitoring or parenteral antimicrobials are admitted to hospitals for inpatient treatment. Hospital-based treatment is reserved for serious infections, and is therefore an important manifestation of disease burden. Pneumonia is a large contributor to pediatric hospitalizations, accounting for 3%-18% of admissions (Madhi et al. 2012).

While less common, invasive pneumococcal disease is associated with high mortality rates. The case-fatality ratio of hospitalized IPD in Europe was 2.4% in children younger than five years of age, 9.1% in individuals 5-64 years of age, and 18.6% in adults 65 years of age and older (Torné et al. 2014).

We report the results of two separate population-based studies that estimate the impact of PHiD-CV10 on hospital admissions. The studies used different methods which complemented each other with regards to underlying assumptions, weaknesses and strengths.

### **5.4.1 Impact on hospital admissions for otitis media and its complications (Paper V)**

The impact of PHiD-CV10 on pediatric hospital admissions for otitis media was examined in paper V. Hospital admissions for otitis media were compared between the vaccine eligible and non-eligible birth-cohorts using a Cox regression model, resulting in a statistically significant 43% estimated vaccine impact. However, this difference seemed to be largely driven by a sharp decrease in the incidence of otitis media associated hospitalization between the first two vaccine non-eligible cohorts (2005 and 2006). This decrease occurred before even selective vaccination of high-risk children was common practice, and several years before the introduction of PHiD-CV10.

Four observational studies that estimate the impact of PCV on otitis media associated hospitalizations have previously been published (Durando et al. 2009; Gisselsson-Solen 2017; Marom et al. 2017; Tawfik et al. 2017). A retrospective study in the United States reported a 66% relative risk reduction in hospitalizations in the period following the introduction of PCV13, compared to the period prior to PCV7 introduction – nine years apart (Tawfik et al. 2017). No attempt was made to correct for secular trends. The study did not include a single observational year prior to the introduction of PCV7 in 2000. The included figures revealed that the entire observed decrease

occurred in the first year of the study, between 2000 and 2001 (Tawfik et al. 2017). Gisselsson-Solen (2017) similarly reported a 42% reduction in AOM associated admissions in a period following the introduction of higher valent PCV compared to the period prior to the introduction of PCV7. The influence of secular trends was not discussed or adjusted for, and the figures revealed that a large portion of the observed decrease occurred immediately following PCV7 introduction. Durando et al. (2009) implemented a pre- and post-cohort design, and compared the rates of otitis media hospitalizations using a simple comparison of means. They included hospitalizations for urinary tract infections as a control, and reported a 36% relative risk reduction. Trends were not considered. Finally, Marom et al. (2017) did not observe a decrease in hospitalizations.

A careful examination of our results does not suggest an observable decrease in otitis media associated hospitalizations in Iceland that can be attributed to the introduction of PHiD-CV10 into the pediatric vaccination program. This is largely congruent with the results of previous studies despite their variable interpretation. Our findings underscore the importance of carefully considering the results of vaccine ecology studies, as secular trends may exert great influence over a long time period.

#### **5.4.2 Impact on pediatric pneumonia hospitalizations (Papers V and VI)**

The impact of PHiD-CV10 on pneumonia hospitalizations was reported in two population-based studies, papers V and VI.

Four randomized trials have evaluated the efficacy of PCV for clinical pneumonia and their results are summarized Table 4. (S. B. Black et al. 2002; Cutts et al. 2005; Kilpi et al. 2018; Tregnaghi et al. 2014). Only Kilpi et al. (2018) reported efficacy for hospital-diagnosed pneumonia, which was 27%. A systematic review and meta-analysis of observational studies of higher valency PCV examining impact on clinical pneumonia identified 11 studies and concluded that among children aged 24 months and younger, the introduction of PCV resulted in a 17% (95%CI 11% to 22%) reduction in clinical pneumonia (Alicino et al. 2017). Of the observational studies identified by the systematic review, three were population-based (Berglund et al. 2014; Nair et al. 2016; Saxena et al. 2015). Only two studies identified by the review discussed or attempted to adjust for secular trends (Sgambatti et al. 2016; Simonsen et al. 2014).

Paper V reported the impact of PHiD-CV10 introduction on pneumonia hospitalizations among children younger than three years of age, and demonstrated a 20% reduction in pneumonia hospitalizations following the nationwide introduction of PHiD-CV into the pediatric vaccination program. The study adds to a growing body of literature by providing population-based, individual-level observational evidence of PCV impact on pneumonia hospitalizations.

As in any vaccine ecological study, careful consideration must be paid to the possibility of unmeasured variables unrelated to the vaccination which could influence the outcome. Because the study followed all children in Iceland for 11 consecutive birth-cohorts, sampling bias was eliminated. This means that differences in the distribution of risk factors among children in the vaccine non-eligible cohorts compared to vaccine eligible cohorts can only be due to systematic changes in the whole population. We are unaware of any systematic changes that would have reduced the incidence of pediatric pneumonia requiring hospitalization, except for the introduction of PHiD-CV. The Children's Hospital Iceland has remained the only pediatric secondary and tertiary care hospital in Iceland. The proportion of the pediatric population the hospital serves as a primary hospital has increased, rather than decreased during the study period. During the same period, hospital admissions due lower respiratory tract infections other than pneumonia increased by 32% in the vaccine eligible cohorts. This would be expected to increase the susceptibility of children for pneumonia. Despite the strengths of paper V, the lack of adjustment for secular trends remained an important weakness.

In paper VI, a time series methodology was employed, and several different methods used to correct for secular trends as has been previously discussed. Among children zero to four years of age, the posterior estimate of the rate ratio for pneumonia hospitalizations was 0.67, with the 95% credible interval spanning 0.51-1.39. Though the 97.5% credible limit is above the threshold value of one, there is a 94% probability that the rate ratio is lower than one, and a 90% probability that it is lower than 0.83. The cumulative number of prevented hospital admissions for pneumonia in this age-group during the first seven years of the vaccination period was 142 (95% credible intervals -115 to 307) – an impressive decline considering that the baseline rate of pneumonia hospitalization was 65-75 per year in this age-group.

We believe that our methods are considerably more robust than the two previously identified observational studies examining PCV impact that discussed or adjusted for secular trends. Sgambatti et al. (2016) reported the incidence of pneumonia hospitalizations among children two to 35 months of age during the two year period before and after the introduction of PHiD-CV10 in Brazil. They examined whether a trend had occurred in the pre-vaccine period by performing a linear regression and concluded that no trend was detectable and therefore no adjustment necessary. Impact was reported as a simple unadjusted rate ratio between the pre- and post-vaccine period, and was 13%. However, linear trends are difficult to estimate in short seasonal time series, and depend strongly on the included period (Bernal, Cummins, and Gasparrini 2016; Kontopantelis et al. 2015).

Simonsen et al. (2014) reported the incidence of hospital admissions for pneumonia, empyema and invasive pneumococcal disease before and after the introduction of PCV13 using data from a convenience sample of 500 hospitals in the United States. They demonstrated 21% impact of PCV13 on all-cause pneumonia among children younger than two years of age, and a 17% impact among children two to four years of age. The pre-vaccine period used to estimate trends was appropriately long (2005-2012) but the trend was again assumed to be linear. Interestingly, sensitivity analyses revealed that excluding the adjustment for linear trend effaced the estimated impact on all-cause pneumonia among children younger than five years of age. The authors did not provide figures showing the observed number of all-cause pneumonia hospitalizations and estimated trend and readers are therefore unable to verify why this might have occurred. However, one could hypothesize that the linear trend was possibly overestimating the number of hospitalizations that would have occurred in the post-vaccine period, had PCV13 not been introduced.

Contrast this with our study, which estimated the relationship between pneumonia hospitalizations and hospitalizations due to other specific diagnoses (synthetic controls) during the six year pre-vaccine period 2005-2010, and used this relationship to predict the monthly number of pneumonia hospitalizations in the post-vaccine period (2013-2017), had PHiD-CV10 not been introduced. This method does not require trends to be linear and correctly propagates the uncertainty of the prediction by incorporating observed synthetic controls in the post-vaccine period. Our methods are based on Bruhn et al. (2017). In their paper they demonstrate their methodology by analyzing population-based data on pneumonia hospitalizations in five countries; Brazil, Chile, Ecuador, Mexico and the

United States, before and after the introduction of PCV7 and PHiD-CV10. Their data was aggregated to slightly different age-groups. The rate ratio between predicted and observed pneumonia hospitalizations ranged from 0.55 to 0.86 among children younger than 12 months of age and the 95% credible intervals did not cross the threshold value of one. However, the rate ratio for children 12-23 months of age and 25-59 months of age was more variable, ranging from 0.76 to 1.05 and 0.77 to 1.06 respectively. Our results are largely congruent.

Taken together, papers V and VI convincingly demonstrate a robust impact of PHiD-CV10 on pneumonia hospitalizations among Icelandic children. The methods used by each paper complement each other, with both papers offsetting methodological weaknesses of the other. Paper V provides individual-level data on pneumonia hospitalizations among all Icelandic children, and corrects for censoring due to hospitalization, death or emigration, providing accurate time at-risk for the whole population. Paper VI used robust methodology to correct for secular trends that explicitly controls for changes in the rates of hospitalization for indications unrelated to the vaccination. This corrects for both observed trends in pneumonia hospitalizations in the pre-vaccine period and trends in health care utilization in general both before and after vaccine introduction. Both studies are population-based and encompass a 13 year observational period. Our studies add to the current literature by demonstrating a robust, measurable decrease in the incidence of pneumonia hospitalization among children following the introduction PHiD-CV10 into a national immunization program.

#### **5.4.3 Impact on hospital admissions for culture confirmed invasive pneumococcal disease**

Invasive pneumococcal disease represents the most serious manifestation of pneumococcal infection. Randomized controlled trials evaluating PCV for IPD have consistently shown large efficacy for both vaccine-type and all-cause IPD, ranging from 77% to 100% and 46% to 93% respectively (Black et al. 2000; Cutts et al. 2005; O'Brien et al. 2003; Palmu et al. 2013; Tregnaghi et al. 2014). The results of the randomized controlled trials are summarized in Table 5.

A large number of observational studies have been published on the impact of PCV on IPD, and their results are considerably more variable than those of randomized trials. Myint et al. (2013) conducted a systematic review of observational studies of the direct impact of PCV7 on vaccine-type and all-cause IPD. The review identified 18 studies which reported the impact on

vaccine-type IPD, which ranged from 39.9% to 99.1%, with a median impact of 90.1%. For the outcome of all-cause IPD, the review identified 30 studies, which reported impact estimates ranging from 1.7% to 80.2% and a median impact of 45.0%. The variation in the study estimates was likely due to variable baseline seroprevalence of vaccine-type pneumococci, vaccine uptake, case-ascertainment, observation period and other methodological differences. Study design was not specifically reviewed (Myint et al. 2013).

We explored the impact of PHiD-CV10 introduction on hospitalized culture-confirmed IPD among vaccine-eligible children in papers V and VI. Both papers utilized culture data from Iceland's reference laboratory at the Department of Clinical Microbiology at Landspítali University Hospital, which receives all invasive pneumococcal isolates for the whole country. Culture data were then cross-referenced with hospitalization records.

In paper V, individual-level population-based data were analyzed by birth-cohort. They were divided into vaccine non-eligible and vaccine eligible cohorts and followed until three years of age. No vaccine-type IPD developed in the 22,336 children in the vaccine eligible cohorts during the 57,507 person-years at-risk. This is compared to 18 vaccine-type IPD hospitalizations during 84,949 person-years at-risk accumulated by the 29,050 children who comprise the vaccine non-eligible cohorts – an incidence rate of 21.2 IPD hospitalizations per 100,000 person-years. The impact of PHiD-CV10 on hospitalized vaccine-type IPD was therefore 100%.

The rate of all-cause IPD decreased from 24.7 (25 hospitalized cases) per 100,000 person-years in the vaccine non-eligible cohorts to 1.71 (one hospitalized case) per 100,000 person-years in the vaccine eligible cohorts. The adjusted hazard ratio was 0.07 (95% CI 0.01-0.50), representing an impact of 93%. These impact estimates compare nicely with the results of randomized controlled trials, and the results of previous observational studies, and adds to the current literature by providing individual-level population-based evidence of extensive protection against IPD (Myint et al. 2013). However, the methods used in paper V were unable to correct for secular trends, and a slight decreasing trend in the incidence of IPD had been observed in the pre-vaccine period.

Paper VI used a time series methodology to estimate the impact of PHiD-CV10 on IPD among children zero to four years of age, adjusting for secular trends in IPD and all-cause hospital admissions. Due to the extremely low event-rate, and the statistical uncertainty introduced by including the contribution of secular trends, the credible intervals of the rate ratio were

wide. The rate ratio between observed and predicted IPD hospitalizations was 0.27 (95% credible interval 0.05-3.00). However, the results were consistent with a 90% probability that the rate ratio was equal to or less than 0.75 and a 93% probability that the rate ratio was lower than one.

The cumulative number of prevented IPD hospitalizations was 14 (95% credible intervals -2 to 67). There was a 90% probability that the vaccine had prevented seven or more IPD hospitalizations. Because aggregate data were analyzed, the number of IPD hospitalizations occurring in the post-vaccine period was three, compared to one in paper V. This is due to several factors. The aggregated age-group included more children (zero to four years of age, compared to zero to two years of age in paper V), and person-time at-risk was not censored due to immigration or emigration.

Taken together, papers V and VI demonstrate a large impact of PHiD-CV10 on vaccine-type and all-cause IPD among vaccine eligible children. Our results represent the highest quality of observational evidence. The outcome measure of culture proven IPD is specific and sampling bias is not possible do to the population-based nature of the data. The observational period is long compared to previous studies, which allows adequate estimation of trends (Myint et al. 2013). Paper V provides individual-level evidence and allows accurate estimation of rates because of careful censoring of person-time. Paper VI adds to this by adjusting for secular trends in both rates of IPD and all-cause hospitalizations. ### Evidence of herd-effect of PHiD-CV10 on pneumonia hospitalization in the unvaccinated population (Paper VI)

To our knowledge, only seven previous publications have examined the herd-effect of pneumococcal conjugate vaccines on pneumonia hospitalizations among the unvaccinated population (Andrade et al. 2017; Bruhn et al. 2017; Griffin et al. 2013; Grijalva et al. 2007; Jardine, Menzies, and McIntyre 2010; Simonsen et al. 2011, 2014), five of which were identified by a recent systematic review (Tsaban and Ben-Shimol 2017). Two of the included studies, Simonsen et al. (2011) and Griffin et al. (2013), did not adjust for trends. The results of the remaining five publications generally showed a reduction in the incidence of pneumonia hospitalizations in children zero to four and five to 17 years of age, and among adults 18-39 and 40-64 years of age, though the exact bounds of the age-groups and point-estimates varied between studies. Impact estimates ranged from 3% to 24% among five to 17 years of age; 0% to 26% among adults 18-39 years of age; and 0% to 19% among adults 40-64 years of age. All but two of the studies suggested

an impact among adults 65 years of age and older, with estimates ranging from 3% to 15%, though none reached significance at the pre-specified alpha of 0.05. Bruhn et al. (2017) reported the impact of PCV on pneumonia hospitalizations in five countries and divided the oldest age-group into adults 65-79 years of age and adults 80 years of age and older. Using a sophisticated synthetic-control methodology, they did not find evidence of impact among these age-groups. The results of Andrade et al. (2017) stand out from the rest, reporting a statistically significant 16% increase in pneumonia hospitalizations among adults 65 years of age and older following the introduction of PHiD-CV10 into the national immunization program in Brazil. They discuss this in detail citing a baseline increasing trend in this age-group prior to vaccine introduction.

The herd-effect of PHiD-CV10 on pneumonia hospitalizations in Iceland was examined in paper VI. Determining the etiology of pneumonia is often difficult as direct sampling of lung tissue is not feasible (Cilloniz et al. 2016; Feikin et al. 2017). In a prospective study of 310 consecutive pneumonia hospitalizations at Landspítali University Hospital in 2008, a potential causative pathogen was only identified in 52% of admissions, despite the active gathering of blood and sputum cultured, oropharyngeal swabs for polymerase chain reaction analysis and urine for antigen testing (Bjarnason et al. 2018). Because of this, and because the results were later to be used in a cost-effectiveness analysis, we used the most sensitive but least specific outcome measure of all-cause pneumonia. We employed a time series methodology to adjust for both secular trends in the outcome measure and trends in hospitalizations for other indications, and demonstrated a robust impact on pneumonia hospitalizations in children five to 19 years of age (26%), and adults 20-39 (32%), 65-79 (25%) and 80 years of age and older (24%) (Bruhn et al. 2017; Shioda et al. 2018). Additionally, the data indicated an 8% impact among adults 40-64 years of age and were compatible with a 77.5% probability that the impact was equal to or larger than 1%. The posterior estimate of impact for children five to 19 years of age was compatible with a 90% probability that the impact was equal to or larger than 1%. Likewise, among adults 20-39, 65-79 and 80 years of age and older, the results were compatible with a 98.5%, 96% and 96% probability that the impact was equal to or larger than 1%.

Our findings of herd-effect among adults older than 65 years of age are discordant with Bruhn et al. (2017) – a publication that introduces some of the methods used in our study. There are several possible reasons for this disagreement. Our study examined the impact of PHiD-CV10, while theirs

was primarily a study of PCV7. In Iceland, the uptake of PHiD-CV10 was immediately high, achieving over 97% uptake of the primary doses in the vaccine eligible birth-cohorts. Contrast this with the United States where uptake of two primary doses was initially 18% in 2002 and increased to 46% in 2004, which was the final year included in Bruhn et al. (2017; McLaughlin et al. 2016). For the other countries included in Bruhn et al. (2017), uptake for three doses during the first year of PCV introduction was 9% in Mexico, 17% in Ecuador, 55% in Chile, and 82% in Brazil (Oliveira et al. 2016). We included seven years of data following vaccine introduction, compared to two to five years of post-vaccine data in Bruhn et al. (2017). This allowed for a longer period for herd-effect to develop and present itself. We fitted four different models to the data (of which the synthetic control model of Bruhn et al. (2017) was one) and produced a final stacked model by maximizing the leave-one-out cross-validation likelihood in the pre-vaccine period. This produced the optimal model, given the pre-vaccine data.

Our results provide robust evidence for the existence of herd-effect on pneumonia hospitalizations following the introduction of PHiD-CV10 into a national immunization program. They support the findings of previous studies that have indicated herd-effect, and improve on them in many ways. The data underlying the study were population-based excluding the possibility that selection bias confounded our findings, and the results were adjusted for secular trends in hospitalization rates and the pre-vaccine incidence of pneumonia. As did all previous studies, the largest and most robust indirect decrease in pneumonia hospitalizations was noted among adults 18-39 years of age. According to Statistics Iceland, the median age at which Icelandic mothers give birth to their first child is 27 years of age. When all births are considered, the median age of mothers and fathers are 29 and 32 years of age respectively. Furthermore, data provided by Statistics Iceland shows that this age-group consistently represents 50% of all daycare staff in Iceland. Adults 18-39 years of age are therefore the primary providers of care for young children and would be expected to benefit the most from indirect protection, as is confirmed by our study. Though purely speculative, the relatively small indirect impact among adults 40-64 years of age could possibly be explained by this age-group having little direct contact with young children. They could represent adults who are unlikely to have young children of their own, and are on average at the height of their professional careers, limiting direct care of grandchildren. This might also explain why the indirect impact increases again among adults 65-79 years of age. The proportion of grandparents would be higher, parents would be entering the height of their

own careers and grandparents would at this age possibly have more leeway to provide direct care as needed.

#### **5.4.4 Evidence of herd-effect of PHiD-CV10 on hospital admissions for invasive pneumococcal disease in the unvaccinated population (Paper VI)**

The herd-effect of pneumococcal conjugate vaccines on invasive pneumococcal disease has been extensively studied. Two systematic reviews identified 262 observational studies published between 1 January 1994 and 6 January 2016 that examined the direct and indirect impact of PCV on vaccine-type and all-cause IPD (Davis et al. 2013; Shiri et al. 2017). No summary of the included studies was attempted by Davis et al. (2013). To our knowledge, only two of the 262 included studies adjusted for pre-vaccine trends (Andrade et al. 2016; Moore et al. 2015).

The publication by Shiri et al. (2017) was also a meta-analysis, which used a Bayesian mixed-effects model to translate the included studies into a single estimate. For each age-group, they reported the yearly risk ratio of IPD among unvaccinated individuals in the post-vaccine period compared to the pre-vaccine period. They also reported the cumulative reduction of IPD as a function of years since PCV introduction and predicted the mean time until a 50% and 90% reduction in IPD was achieved. The study demonstrated a yearly post-vaccine risk ratio of vaccine-type IPD of 0.79 (95% credible intervals 0.75-0.81), translating to a mean period to attain a 50% population reduction of vaccine-type IPD of 2.3 years (95% credible interval 1.9-2.7), and 8.9 years (95% credible interval 7.8-10.3) to attain a 90% reduction. When stratified by age-group, the yearly risk ratio of vaccine-type IPD was 0.77 among adults 65 years of age and older, and the time until 50% and 90% reduction was 4.1 and 10.3 years respectively.

Interestingly, the results for all-cause IPD were different. The yearly risk ratio for all age-groups was 0.99 (95% credible intervals 0.96-0.99) and the time until 50% and 90% reduction were not estimated, presumably due to the credible intervals approaching infinity, though this was not commented on in the paper or supplementary files. When stratified by age-group, a mean 50% reduction of all-cause IPD was achieved 12 years after the introduction of PCV in children younger than five years of age, children five to 18 years of age and adults 19-49 years of age. Among adults 50-64 years of age, the mean reduction at 12 years was 39%, but the 95% credible interval included 50%. However, among adults 65 years of age and older, the mean predicted

reduction at 12 years was 30% and the 95% credible intervals did not include 50%.

The indirect effect of PHiD-CV10 on IPD hospitalizations in Iceland was studied in paper VI. Because the data in paper VI were meant to inform a subsequent cost-effectiveness analysis, and serotype replacement is known to blunt the impact of PCV, we only studied all-cause IPD (Weinberger, Malley, and Lipsitch 2011). Because only 338 IPD hospitalizations occurred during the whole study period, we were only able to estimate impact among few age-groups and data were aggregated by year-quarter instead of by month.

We demonstrated that among individuals five to 64 years of age, the introduction of PHiD-CV10 prevented 29 (95% credible interval 1 to 65) cases of IPD serious enough to warrant hospital admission in the first seven years of the immunization program. Before the vaccine introduction, this population experienced 16 IPD hospitalizations per year. The rate ratio between the observed and predicted number of IPD hospitalizations was 0.44 (95% credible intervals 0.31-0.68), which translates to a 56% vaccine impact in this age-group and is compatible with a 99% probability that the impact is equal to or larger than 1%. Examination of the rolling rate ratio presented in Figure 34, shows that impact was first detectable in the latter half of 2013, and achieved a 50% reduction in the beginning of 2014.

Conversely, the evidence of herd-effect among adults 65 years of age and older was less clear. The cumulative number of prevented cases were 10 (95% credible intervals -16 to 45) and rate ratio was 0.94 (95% credible intervals 0.62-1.53), which is consistent with a 50% probability that the vaccine impact was 6% or larger in this age-group, and a 62.5% probability that the impact was equal to or larger than 1%. Examination of the rolling rate ratio presented in Figure 34 does not seem to suggest that the impact is increasing as time passes from the vaccine introduction.

Our study adds to the current literature by presenting population-based data and taking into account secular trends prior to vaccine introduction. Our findings are largely congruent with previous studies examining the herd-effect of PCV on all-cause IPD. We show a robust indirect protection among individuals five to 64 years of age, after adjusting for any secular trends in the pre-vaccine period, and the result is consistent with visual examination of the raw data (Figure 31). This is an important finding for policy decisions, as this age-group represents the population of working adults in any given country. Though our findings are consistent with slight decrease in IPD

hospitalizations among adults 65 and older, the effect is not as obvious. While surprising, this result is consistent with the literature which seems to suggest a large and robust impact on vaccine-type IPD in this age-group, but a marginal impact on all-cause IPD (Davis et al. 2013; Shiri et al. 2017). Though one can only speculate, this may be due to a long tradition of 23-valent polysaccharide vaccination in this age-group in Iceland, as demonstrated by our data.

## **5.5 Cost-effectiveness of introducing PHiD-CV10 into the Icelandic pediatric vaccination program (Paper VI)**

The health care system operates under resource constraints and funding must be optimally allocated to maximize the benefit for the population. Cost-effectiveness analyses are one of many tools that can be used to inform policy decisions in this regard (Gray et al. 2011). A large number of cost-effectiveness analyses of pneumococcal conjugate vaccines have been published (Saokaew et al. 2016; Vooren et al. 2014; Wu et al. 2015). Of those, 21 studies examined the cost-effectiveness of PHiD-CV10 or PCV13 (Blank and Szucs 2012; By et al. 2012; Castiglia et al. 2017; Chuck et al. 2010; Delgleize et al. 2016; Díez-Domingo et al. 2011; Earnshaw et al. 2012; Gouveia et al. 2017; Klok et al. 2013; Knerer, Ismaila, and Pearce 2012; Kuhlmann and Schulenburg 2017; Newall et al. 2011, 2016; M. A. O'Brien et al. 2009; Robberstad et al. 2011; Rozenbaum et al. 2010; Rubin et al. 2010; Strutton et al. 2012; Talbird et al. 2010; Hoek, Choi, et al. 2012; Zhou et al. 2014). The methodology employed by each study was reviewed extensively in chapter 1.3. Each found the pneumococcal conjugate vaccine to be cost-effective compared to no vaccination.

We reported the cost-effectiveness of introducing PHiD-CV10 into the Icelandic vaccination program. Cost-effectiveness was evaluated from both the health care and societal perspectives. Though we did directly measure vaccine uptake and serotype coverage, we did not need to explicitly model these variables as the study's ecological design implicitly captured their effects. The pre- and post-vaccination incidence of otitis media, inpatient pneumonia and IPD were directly measured in the population, and a previously published Bayesian time series methodology was employed to estimate what the incidence would have been, had the vaccine not been introduced (Bruhn et al. 2017, Shiota et al. 2018). These methods resulted in a posterior predictive distribution, which allowed us to estimate uncertainty empirically, and avoid the need for assuming an arbitrary uncertainty distribution.

Costs associated with the administration of the vaccine were directly obtained from the Directorate of Health and not based on assumptions or list pricing. The direct costs associated with the outcome were sampled from individual-level otitis media visits, and hospital admissions for pneumonia and IPD. The distribution was empirically estimated through resampling of the observed costs, again allowing us to avoid assuming arbitrary uncertainty distributions. Days of work lost due to hospitalized pneumonia and IPD were modeled as a function of the individually observed hospital lengths of stay and the distribution was estimated through direct resampling. All cost and outcome data were included in an overall Bayesian model, which propagated the uncertainty of each of the model parameters and produced a posterior distribution of the cost-effectiveness that includes an empirical probabilistic sensitivity analysis.

Our results showed that the introduction of PHiD-CV10 was cost-saving by 7,463,176\$ in constant 2015 USD from the health care perspective. The direct cost of introducing the vaccine was 2,652,364\$ as of 31 December 2015. However, this cost was offset by the cost-savings associated with averted otitis media visits, pneumonia admissions and hospitalized IPD, which totaled 10,115,540\$. When the societal perspective was considered, and averted lost workdays were also included, the vaccine introduction was cost-saving by 8,164,894\$. The direct savings resulting from vaccine-prevented cases of AOM was 1,389,900\$. The incremental cost-effectiveness ratio per prevented case of AOM was -543\$ (95% credible interval -1,508\$ to -48\$) – that is, the health care system's monetary gains exceeded the initial expenditure, resulting in each additional case averted saving rather than costing money. Similar numbers were seen for hospitalized disease. The ICER for each additional prevented pneumonia hospitalization was -5,640\$ (95% credible interval -10,336\$ to -1,032\$) and -119,992\$ (95% credible interval -387,183\$ to -9,542\$) per prevented IPD hospitalization.

Our results are quantitatively similar to the body of cost-effectiveness literature of PCV. Most show that introducing PCV into national immunization programs is cost-effective when compared to no vaccination. However, our study improves on prior studies in several important ways. We included more granular data than have previously been incorporated into a cost-effectiveness analysis of PCV. Because they are in essence predictive models, cost-effectiveness analyses are particularly sensitive to the accuracy of the modelling assumptions (Gray et al. 2011). Most of the prior studies did not collect detailed data on vaccine uptake, serotype coverage, incidence of

disease in the population, disease sequelae, or direct and indirect costs (Vooren et al. 2014; Wu et al. 2015). Efficacies were based on the results of randomized controlled trials, but the existence and magnitude of herd-effect and serotype-replacement were usually based on assumptions and expert opinion (Vooren et al. 2014; Wu et al. 2015). Utilities were invariably based on studies conducted in other populations and time-periods (Herdman et al. 2016). Contrast this with our study, in which all inputs were directly measured in the population.

Our study included a built in probabilistic sensitivity analysis of all parameters using empirically derived distributions. In general, a sensitivity analysis is necessary to explore the cost-effectiveness outcomes over a range of plausible input parameters, due to the subjective nature of underlying assumptions. Consensus statements from the World Health Organization and the International Society for Pharmacoeconomics and Outcome Research (ISPOR) require, at minimum, a one-way sensitivity analysis of each of the modelling assumptions (Mauskopf et al. 2018; Walker, Hutubessy, and Beutels 2010). Despite the considerable uncertainty associated with utilities, they were often not examined with sensitivity analyses (Blank and Szucs 2012; Chuck et al. 2010; Earnshaw et al. 2012; Gouveia et al. 2017; Klok et al. 2013; Newall et al. 2016; Strutton et al. 2012; Talbird et al. 2010). Similarly, cost inputs that were often purely assumed, based on expert opinion, or based on national tariffs given without any reference, were in many studies not included in a sensitivity analysis (Chuck et al. 2010; Earnshaw et al. 2012; Gouveia et al. 2017; Klok et al. 2013; Newall et al. 2016; Strutton et al. 2012; Talbird et al. 2010).

Our study is inherently different than most previous studies, in that it examines the cost-effectiveness of an intervention that has already been introduced. The most obvious strength of a post-implementation ecological design, is that it absolves the need to rely on untestable assumptions regarding herd-effect and serotype-replacement, which are instead directly observed. To our knowledge, only one previous study has reported the post-implementation cost-effectiveness of PCV (Newall et al. 2016). They used a time series methodology, but with access to only three years of annual pre-vaccine incidence rates, they were unfortunately only able to make crude adjustments and were not able to leverage the strengths of the post-implementation approach, as they acknowledge in the discussion chapter.

Our study improves on the current literature by providing post-implementation evidence of the cost-effectiveness of PHiD-CV10. We

demonstrate a large cost-savings that is robust with regards to extensive sensitivity analysis of all parameters. Our results demonstrate that initially expensive vaccine interventions can be shown to produce such a decrease in health care consumption, that the resulting cost-savings offset the initial cost – all the while resulting in reduced suffering in the population. Our study highlights the importance of careful post-implementation studies; both as a tool to validate and calibrate the predictions made by pre-implementation cost-effectiveness studies, which rely heavily on unverifiable assumptions, and to provide evidence of vaccine benefit for policy makers.

## **6 Conclusions**

All the aims of the thesis proposal were met. The impact of PHiD-CV10 introduction into the pediatric vaccination program in Iceland was demonstrated on several facets of pneumococcal disease.

### **6.1 Direct and indirect impact on otitis media**

The introduction of PHiD-CV10 resulted in a decrease in rate of acute otitis media in primary care.

Among children younger than three years of age, the impact of PHiD-CV10 on AOM episodes was 21%. The mean number of AOM episodes per child decreased from 1.6 to 1.3 by their third birthday, and the relative proportion of children who never experienced an episode increased by 14%. The incidence rate of AOM decreased from 45 to 40 episodes per 100 person-years. The vaccine independently protected against a child's first (15%) and second (5%) episode of AOM, but in the subgroup of children who had already experienced two, no additional protection was evident. After secular trends in the rate of AOM visits to primary care had been taken into account, and trends in visits for other indications adjusted for, the impact among children younger than one, one, two, and three to four years of age was 26%, 28%, 12% and 14% respectively. In children younger than five years of age, PHiD-CV10 prevented 11,638 AOM visits during the first five years of the vaccination program.

Herd-effect was demonstrated for AOM following the introduction of PHiD-CV10. Among children younger than four months of age, who were too young to receive direct benefit from the vaccine, the impact on AOM was 40%. Among children five to nine, 10-14 and 15-19, the impact was 12%, 17% and 11% respectively during the first five years of the vaccination program, after adjusting for secular trends in both AOM visits and visits for other indications. None of the children in these age-groups were eligible for the PHiD-CV10 vaccination program and no catch-up program was implemented in Iceland.

### **6.2 Direct impact on antimicrobial consumption**

Antimicrobial consumption decreased following vaccine introduction. Among children younger than three years of age, the impact of PHiD-CV10 on all-cause outpatient antimicrobial consumption was 8%. The incidence rate of antimicrobial prescriptions was 165 per 100 person-years before the vaccine

introduction, which decreased to 150 per 100 person-years. The proportion of children in the vaccine non-eligible cohorts and vaccine eligible cohorts who filled at least one antimicrobial prescription by three years of age was 88.6% and 86.8% respectively. The mean number of prescriptions per child by their third birthday decreased from 6.5 to 5.8 among boys, and from 6.1 to 5.4 among girls. The relative proportion of children who never filled an antimicrobial prescription was 16%. An independent vaccine impact was still discernible in children who had filled up to three prior antimicrobial prescriptions. When only AOM-associated antimicrobial prescriptions were considered, the vaccine impact was 21%. The proportion of AOM visits resulting in antimicrobial prescription remained fairly stable between 57% and 64%, suggesting that the observed decrease in antimicrobial consumption is due to a decrease in disease frequency rather than changes in prescribing habits.

The introduction of PHiD-CV10 resulted in a decrease in AOM requiring parenteral antimicrobial. The vaccine impact on AOM episodes treated with ceftriaxone was 52% among children zero to four years of age. Some of the observed decrease was due to a 12% vaccine impact on overall AOM visits to the pediatric emergency department, which decreased from 47.4 visits to 41.8 per 1,000 person-years. However, among the subset of Icelandic children who presented to the pediatric emergency department with AOM, the vaccine decreased the proportion that required treatment with ceftriaxone by 42%. A decrease in ceftriaxone use for other causes was not observed, and overall ceftriaxone remained the same in other age-groups.

### **6.3 Direct impact on tympanostomy tube placements**

Tympanostomy tube placements increased despite the inclusion of PHiD-CV10 into the national pediatric vaccination program. The cumulative incidence of tympanostomy procedures by five years of age increased from 29% in the 2005 birth-cohort, to 31% in the 2012 cohort. The median age of children undergoing their first tympanostomy procedure was 17 months, and 18% were younger than one year of age. The proportion of children who did not have a single recorded otitis media associated primary care visit before the undergoing the procedure increased from 21% to 29%, and the proportion of children who had never filled an antimicrobial prescription increased from 3% to 5%. It remains unclear why the rate of tympanostomy procedures increased following PHiD-CV10 introduction, despite the lower incidence of acute otitis media, otitis media, and antimicrobial prescriptions.

## **6.4 Direct and indirect impact on pneumonia hospitalizations**

The introduction of PHiD-CV10 resulted in a decrease in pneumonia hospitalizations. Among children zero to three years of age, the vaccine impact on pneumonia hospitalizations was 20%. The hazard of pneumonia among vaccine eligible and vaccine non-eligible children began to deviate at twelve months of age. This occurred despite an increase in hospitalizations for other lower respiratory infections in the same children between zero to five months of age. Because pneumonia and other lower respiratory tract infections share common risk factors, the results do not suggest that the observed decrease in pneumonia hospitalizations was confounded by changes in unmeasured risk factors. After secular trends in the rate of pneumonia hospitalizations and hospital admissions for other indications had been adjusted for, the impact of PHiD-CV10 on pneumonia hospitalizations among children zero to four years of age was 33%.

Herd-effect was demonstrated for pneumonia hospitalizations following the introduction of PHiD-CV10. Taking into account secular trends in hospitalizations regardless of indication, the impact of PHiD-CV10 on pneumonia hospitalizations was 26% among children five to 19 years of age, 32% among adults 20-39, 8% among adults 40-64, 25% among adults 65-79, and 24% among adults 80 years of age and older. To our knowledge, the methodology adequately adjusted for all possible confounders and sensitivity analyses supported the robustness of the results.

## **6.5 Direct and indirect impact on hospital admissions for invasive pneumococcal disease**

PHiD-CV10 introduction resulted in both direct and indirect impact on hospitalized invasive pneumococcal disease. No vaccine-type IPD was observed in the vaccine eligible cohorts following the introduction of the vaccine. The impact of PHiD-CV10 on IPD among children zero to three years of age regardless of serotype was 93%. After secular trends in the rate of IPD hospitalizations regardless of serotype had been taken into account, the impact among children zero to four years of age was 63%. The trend adjusted impact was heavily dependent on which method was used to adjust for trend, likely due to the small number of IPD hospitalizations. If adjustments for hospitalizations for other indications were also included the impact was 90%. The impact on IPD hospitalizations among individuals five to 64 years of age was 56% and the results were not dependent on the method used to adjust for secular trends. Conversely, the impact IPD

regardless of serotype was consistently small (6%) among adults 65 years of age and older compared to other age-groups, regardless of the adjustment method used. This finding is consistent with prior studies, and in the case of Iceland, may be due to a long tradition of pneumococcal vaccination in this age-group.

## **6.6 Cost-effectiveness of PHiD-CV10 introduction**

The introduction of PHiD-CV10 was not only cost-effective but cost-saving during the first five years of the program. From the health care perspective, the program was cost-saving by 6,722,048\$. The incremental cost-effectiveness ratio per prevented case of AOM was -488\$, which implies that after considering all costs associated with purchasing the vaccine, the total cost of preventing a case of AOM was negative – 488\$ were saved rather than spent. The ICER for each prevented pneumonia hospitalization was -5,640\$ and was -105,548\$ per prevented IPD hospitalization. When work-loss was also considered, the program was cost-saving by 7,404,352\$ and the ICER for AOM, hospitalized pneumonia and hospitalized IPD were -541\$, -6,309\$ and -116,809\$ respectively. Mortality, disease sequelae, and quality of life were not considered in our study. These estimates include all the associated costs of the vaccine program, but not all the benefits, and are therefore likely underestimates of the true vaccine benefit.

## **6.7 Future research questions**

The findings of this work have raised further questions that may be answered with the data collected by our research group, and others that may require further data collection. Through careful study design these questions will in the future be answered by our research group.

### **6.7.1 What is the relationship between the age of a child at the time of their first episode of acute otitis media and their future risk of recurrent or protracted disease?**

Answering this question with population-based data requires a careful approach to untangle true increases in risk from confounded results. Health-seeking behavior would need to be adjusted for, as this could both independently increase the probability of being diagnosed with early AOM, and the probability of subsequently being diagnosed with repeated AOM and receiving tympanostomy tubes. Our interest in the question is both because we would like to provide evidence for or against the hypothesis that early insult to the middle ear mucosa increases risk of further disease, and

subsequently whether delaying a child's first episode of AOM could decrease their risk of future disease. Several approaches would need to be used. To ascertain whether an early episode of AOM increased this risk, rather than an early episode of any infectious visit to primary care, we could use urinary tract infections as a control. The question could then be restated as: how much greater is the subsequent risk of recurrent AOM and tympanostomy tube procedures among children who experienced an early episode of AOM, compared to children who experienced an early urinary tract infection? The analysis could possibly leverage the month of birth as an instrumental variable to estimate the causal effect, however this would need to be examined further before implementation. Sensitivity analysis would explore varying definitions of the exposures and outcome.

#### **6.7.2 To what degree, if any, did physicians change their prescribing habits for AOM following the introduction of a universal pneumococcal vaccination program?**

This question could be answered with the data that we have currently collected. Episodes of AOM would need to be scrutinized. Repeated visits for the same episode would need to be delineated from visits representing a new episode. A child presenting with AOM who then re-visits three days later only then receiving an antimicrobial prescription would need to be categorized differently than a child who received a prescription on the day of their first visit. Two approaches would be taken that would complement each other. The first would ask whether the proportion of children who presented with AOM and did not receive an antimicrobial prescription increased overall, regardless of the identity of the physician. The proportion of children who received a watchful waiting approach would also be analyzed. The second approach would examine the same indices, but from the perspective of individual physicians. Our data include the physician identification number of all primary care physicians who diagnosed AOM during an 11 year period. We could select all physicians who had diagnosed and treated AOM in primary care for at least three years before and after the introduction of PHID-CV10, and within this group ask whether the prescribing habits changed. Urinary tract infections could be used as a control for both approaches, to better ascertain whether any observed effect was due to the vaccine. Time series methods would be used to adjust for secular trends.

#### **6.7.3 What is the incidence of AOM with treatment failure and has it changed following vaccine introduction?**

We have already presented evidence of impact on AOM with treatment failure, by using ceftriaxone treatment episodes as a proxy. This question could be answered more robustly by using our full population-based data. Time series methods would be used to adjust for secular trends. Because AOM with treatment failure is not strictly defined though intuitive to understand, several different definitions would be tested. This would include repeated visits and repeated antimicrobial prescriptions, repeated antimicrobial prescriptions only, a repeated visit with the diagnosis of tympanic membrane rupture, a repeated visits with a subsequent first prescription for otological antimicrobial ear drops in a child without a tympanostomy tube, a repeated visit to the pediatric emergency department with a AOM associated diagnosis, hospital-based treatment with parenteral antimicrobial, hospital admission with an AOM associated diagnosis, and a diagnosis of mastoiditis. These data can be linked to the microbiological database of the Department of Clinical Microbiology at Landspítali University Hospital to ascertain which pathogens were detected in the subset of children with treatment failure who underwent tympanocentesis. The database includes all clinical cultures taken in Iceland.

#### **6.7.4 What is the incidence and cumulative incidence of tonsillectomies in young children in Iceland?**

Our results revealed that the incidence of tympanostomy tube placements among Icelandic children are the highest in the world. Some have suggested that the high cumulative incidence among Icelandic children may be due to genetically influenced traits in the middle ear that result in one third of children requiring this procedure. We disagree. Rather, we believe this to be a result of a system that bases reimbursement on the completion of procedures and does not require a referral from another physician to do so. If we are correct, we should see a similarly high incidence and cumulative incidence of tonsillectomies as tympanostomy placements.

#### **6.7.5 Do children experience fewer episodes of AOM after undergoing a tympanostomy tube placement than they would otherwise have experienced?**

Based on our clinical experience and the discourse we observe both within the health care system and media in general, we believe that the great majority of tympanostomy tube procedures are performed on the premise that they will decrease the subsequent number of AOM episodes. This could be tested using an Andersen-Gill model with time-varying variables. This approach would reveal what impact undergoing a tympanostomy tube

procedure has on subsequent episodes of AOM compared to children who did not undergo the procedure, after adjusting for age, gender and the previous number of AOM episodes. Several different case definitions could be used to explore whether this has an effect on the result. Children who have undergone a procedure may be more likely to consult the otolaryngologist for a subsequent acute symptomatic disease, rather than presenting to primary care. These visits would not be included in our data and this possibility would need to be controlled for. One way would be to include examine the outcome of pharyngitis and tonsillitis. These infections represent acute symptomatic disease that an otolaryngologist may be consulted for, but would not be expected to be influenced by undergoing a tympanostomy tube placement. If the number of pharyngitis and tonsillitis cases decrease following the procedure, this would suggest children are increasingly consulting private practice otolaryngologist and any observed effect on AOM episodes must be interpreted accordingly. Another way of adjusting for this bias would be to examine the effect of the procedure on all-cause antimicrobial prescriptions, as the National Drug Prescription Registry contains all prescriptions, regardless of provider.

#### **6.7.6 Would tympanostomy tube procedures have increased to a larger degree, had PHiD-CV10 not been introduced into the pediatric vaccination program?**

The increase in tympanostomy procedures seen in our study was surprising and unintuitive in the context of large decreases in AOM and antimicrobial prescriptions. Tonsillectomies represent a perfect control for tympanostomy procedures within a time series framework. Tonsillectomies are performed by the same specialist physicians, and are therefore subject to the same variables influencing access to the procedure; the number of practicing otolaryngologists, the ease of obtaining an appointment, the number of available operating room slots, and the individual threshold of the surgeon to operate. Parents would be expected to have similar reservations and expectations for both procedures. From their perspective, both are procedures that are meant to prevent repeated bouts of symptomatic infection, they both require general anesthesia, and both are associated with a slight risk of complications. Furthermore, while PHiD-CV10 would be expected to influence the rate of tympanostomy tube procedures, it would not influence tonsillectomies. Therefore, a time series model which establishes the relationship between tonsillectomies and tympanostomy tube procedures in the pre-vaccine period, and adjusts for the trajectory of in the secular trends of each procedure, would add to our knowledge of how the incidence

of tympanostomy tube placements would have developed, had the vaccine not been introduced.

#### **6.7.7 What was the direct and indirect effect of PHiD-CV10 on individual and grouped serotypes of invasive pneumococcal disease, after adjustment for secular trends in both IPD and invasive disease caused by other pathogens?**

We have already examined the impact of PHiD-CV10 on all-cause IPD but have yet to examine specific serotypes. This would require more specific synthetic-controls than were used in our previous study and a longer pre-vaccine period. We have access to the microbiological database of the Department of Clinical Microbiology at Landspítali University Hospital, which has recorded all culture data in Iceland from 1985. With this data we could use invasive disease caused by other pathogens as a control, which represent perfect controls for impact studies on invasive disease. Invasive disease caused by other pathogens would not be expected to change due to pneumococcal vaccination, but shares the same risk factors as IPD, and the detection rate of both are concurrently influenced by the propensity to obtain cultures of sick individuals and the ability of the microbiology lab to detect a pathogen in the cultures it receives.

### **6.8 Conclusion**

In conclusion, we have demonstrated large decreases in the incidence of acute otitis media, antimicrobial consumption, pneumonia hospitalizations and invasive pneumococcal disease in vaccine eligible children following the introduction of PHiD-CV10 into the pediatric vaccination program in Iceland. We have also shown a robust herd-effect in acute otitis media episodes among children too young and too old to have received direct benefit from the vaccine, and large decreases in pneumonia hospitalizations and hospitalizations for invasive pneumococcal disease among adults. A robust post-implementation cost-effectiveness study was conducted and found the vaccine program to be cost-saving from both the health care and societal perspectives, even before taking into account long-term sequelae, mortality and quality of life. Data were collected from several population-based registries and included long pre- and post-vaccine periods. The quality of the data, their scope and the analytical methods used allowed us to perform an ecological study that estimated the vaccine impact to previously unattainable degree. The collected data will continue to allow us to answer further

questions regarding the impact of introducing PHiD-CV10 into national vaccine program in Iceland.



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Eythorsson E, Hrafnkelsson B, Erlendsdóttir H, Atli Gudmundsson S, Kristinsson KG, Haraldsson Á. Decreased AOM with Treatment Failure Following Introduction of the Ten-Valent Pneumococcal Haemophilus influenzae Protein D Conjugate Vaccine. *Pediatr Infect Dis J*. December 2017;1. doi:10.1097/INF.00000000000001870.

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Eythorsson E, Hrafnkelsson B, Erlendsdóttir H, Kristinsson KG, Haraldsson Á. Impact and cost-effectiveness of the 10-valent pneumococcal conjugate vaccine in Iceland, a population-based study (Submitted for publication in *BMJ*)



# **Paper I**



## Decreased Acute Otitis Media With Treatment Failure After Introduction of the Ten-valent Pneumococcal *Haemophilus influenzae* Protein D Conjugate Vaccine

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**Background:** Acute otitis media (AOM) nonresponsive to antibiotics is most commonly caused by antibiotic-resistant *Streptococcus pneumoniae* and *Haemophilus influenzae*. A strategy for treating these infections with parenteral ceftriaxone was adopted at the Children's Hospital Iceland. The 10-valent pneumococcal *H. influenzae* protein D-conjugate vaccine was introduced into the vaccination program in Iceland in 2011. The aim was to study its effect on the incidence of AOM with treatment failure.

**Methods:** This retrospective observational study included children who visited the Children's Hospital Iceland because of AOM or received ceftriaxone, regardless of indication from 2008–2015. Incidence rate was calculated for prevaccine (2008–2011) and postvaccine (2012–2015) periods using person-years at risk within the hospital's referral region. Incidence rate ratio of ceftriaxone treatment episodes of AOM was calculated using the Mantel-Haenzel method adjusting for age. Incidence risk ratio of ceftriaxone treatment if presenting to the hospital with AOM was calculated to adjust for rate of AOM visits.

**Results:** Visits for AOM decreased from 47.5 to 33.9 visits per 1000 person-years, incidence rate ratio (IRR) 0.86 (95% confidence interval [CI]: 0.81–0.91),  $P < 0.001$ . Fewer AOM episodes were treated with ceftriaxone, decreasing from 6.49 to 2.96 treatment episodes per 1000 person-years, with an overall Mantel-Haenzel adjusted IRR 0.45 (95% CI: 0.37–0.54;  $P < 0.001$ ). This remained significant after adjusting for the decrease in AOM visits, IRR 0.53 (95% CI: 0.44–0.63;  $P < 0.001$ ).

**Conclusions:** Visits for AOM and ceftriaxone use decreased significantly after *H. influenzae* protein D-conjugate vaccine introduction. The observed decrease in ceftriaxone use is presumed to represent a decline in AOM with treatment failure, secondary to a decrease in resistant infections.

**Key Words:** otitis media, pneumococcal vaccines, *Streptococcus pneumoniae*, ceftriaxone, drug resistance, microbial

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**A**cute otitis media (AOM) is the most common reason for physician visit and outpatient antibiotic prescriptions among children in Iceland and other Western countries.<sup>1–7</sup> Resolution rates

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for AOM with or without treatment are high.<sup>8</sup> However, treatment failures and recurrent resistant infections are well-recognized clinical problems. Treatment failure is defined as the persistence of symptoms 48–72 hours after the initiation of appropriate antibiotic therapy. The most common reason for treatment failure is infection caused by penicillin nonsusceptible *Streptococcus pneumoniae* (PNSP) and *Haemophilus influenzae*.<sup>9–13</sup>

Infections because of multidrug-resistant pneumococci were first reported in 1978.<sup>14</sup> In Iceland, the prevalence of a multidrug-resistant clone of serotype 6B increased rapidly during the late 1980s,<sup>15</sup> which led to an increase in cases of AOM with treatment failure and recurrent AOM.<sup>16</sup> Amoxicillin was subsequently recommended as the first-line treatment, but high-dose treatment had not yet been introduced at that time. As the prevalence of this clone declined, cases of treatment failure likewise dwindled. From 2004 to 2007, the prevalence of another multidrug-resistant clone (serotype 19F) rapidly increased,<sup>17</sup> precipitating another increase in treatment failures, this time often despite high-dose amoxicillin treatment. A strategy for treating these infections with parenteral ceftriaxone (Rocephin, Roche, Denmark) was adopted at the pediatric emergency department at the Children's Hospital Iceland, the only tertiary pediatric referral hospital in Iceland. Although effective, the treatment imposes burdens upon the children as well as upon the Children's Hospital.

Pneumococcal conjugate vaccines (PCV) are directed against the most common pathogenic pneumococcal serotypes. Post-licensure surveillance studies of PCV have shown a decrease in PNSP.<sup>18,19</sup> The 10-valent pneumococcal *H. influenzae* protein D conjugated vaccine (PHiD-CV10; Synflorix, GlaxoSmithKline, Belgium) was introduced into the Icelandic pediatric vaccination program in April 2011. No systematic vaccination against pneumococcus had been implemented before this introduction. From 2007 to 2011, 40.3% of pneumococcal isolates regardless of sampling site and 48.7% of isolates from the middle ear were PNSP. Of those, 93.9% and 97.2%, respectively, were serotypes included in PHiD-CV10.<sup>20</sup>

A retrospective observational study was undertaken to describe the effect of PHiD-CV10 on the incidence of parenteral ceftriaxone treatment of AOM not responding to oral antibiotics. Ceftriaxone use for other indications and in older age groups was evaluated to exclude a universal change in ceftriaxone usage. The rate of visits for AOM was also obtained to exclude the possibility that any changes in ceftriaxone treatment for AOM were because of a change in the number of AOM cases.

## METHODS

### Data Sources

Included in the study were all children <18 years of age who visited the Children's Hospital because of AOM from January 1, 2008, to December 31, 2015. A visit or admission was considered to be because of AOM if it was associated with International Classification of Diseases Version 10 discharge diagnoses of

nonsuppurative otitis media (H65) or suppurative and unspecified otitis media (H66) extracted from the Children's Hospital's electronic medical records. Included were visits to both the emergency department and outpatient clinics of the Children's Hospital, as well as inpatient admissions. The total number of visits to the Children's Hospital, regardless of indication, was obtained from the hospital's database.

Procedural codes that represent the administration of ceftriaxone were extracted from the medical records, along with the International Classification of Diseases Version 10 diagnostic code of the treated disease. Ceftriaxone use was linked to the individual participant using unique government-issued personal identification numbers. Ceftriaxone use for other indications and in older age groups was evaluated to exclude the possibility of a universal change in usage.

For cases of AOM, the Children's Hospital referral region was defined as a driving distance of less than 100 km from the facility. Population demographic information for both this referral region and for the whole country was obtained from Statistics Iceland ([www.statice.is](http://www.statice.is)).

The number of children who were vaccinated with PHiD-CV10 by month was extracted from a centralized National Vaccine Register maintained by the Icelandic Directorate of Health.

### Statistical Analysis

The date of vaccine introduction was used to define pre-vaccine (2008–2011) and postvaccine (2012–2015) periods. Only 16 individuals ≥4 years of age received ceftriaxone for the treatment of AOM during the study period. Primary analysis was, therefore, restricted to children 0–3 years of age.

### Ceftriaxone Treatment Episodes

The total number of AOM episodes treated with ceftriaxone was aggregated by month. An episode was considered distinct if ceftriaxone was administered without documented ceftriaxone use in the preceding 14 days. The same definition was used for the comparative treatment episodes of both pneumonia and for a combined group of all other diagnoses. Ceftriaxone use regardless of indication were calculated for children 0–3, 4–7, 8–11 and 12–17 years of age. IRR was estimated using the Mantel-Haenzel method with stratification by age group.

Pre- and postvaccine incidence rates of ceftriaxone use were calculated by dividing the number of treatment episodes with the

number of person-years at risk in the Children's Hospital referral region. This was done for cases of AOM, pneumonia and all other diagnoses. Age-specific incidence rate ratios (IRR) with Wald confidence intervals (CIs) were calculated between periods and compared using  $\chi^2$  test. Homogeneity of effect between age-strata was determined with  $\chi^2$  tests. If no effect modification was present, an overall IRR was estimated with the Mantel-Haenzel method. Otherwise, an overall crude IRR was calculated.

### Visits due to AOM

Visits for AOM were aggregated by month and considered distinct if the child had no visit for AOM in the preceding 14 days. Pre- and postvaccine incidence rates of AOM visits per 1000 person-years were calculated, and the 2 periods were compared with Mantel-Haenzel IRR and  $\chi^2$  test of significance. To test whether possible changes in ceftriaxone treatments were due only to change in the number of visits for AOM, the incidence risk of ceftriaxone treatment was calculated for both periods, using the number of AOM visits as the denominator. Incidence risk ratio between periods was found using the Mantel-Haenzel method with age strata unless effect modification was present.

## RESULTS

A total of 117,250 visits to the Children's Hospital for any indication were recorded from 2008 to 2015. Seasonal variation in the number of these visits was apparent, with an increase in visits during the winter months of October through March compared with that in April through September. The total number of visits grew steadily from 12,229 in 2008 to 14,502 in 2015. During the same period, 4624 children <4 years of age visited the Children's Hospital 6232 times for the treatment of 4994 distinct episodes of AOM, of which 531 episodes were treated with ceftriaxone.

The number of children <18 years of age living within the Children's Hospital's referral region was stable during the study period decreasing from 62,067 in 2008 to 61,798 in 2015. The number of children <4 years of age in the same region increased from 13,562 in 2008 to 14,644 in 2011 and then decreased again to 13,272 in 2015. Raw incidence rates of total visits, visits for AOM and parenteral ceftriaxone use are shown in Table 1.

### Vaccination Rates

The percentage of children <4 years of age who had received ≥2 doses of PHiD-CV10 by December of each year was 0.4% in

**TABLE 1.** Incidence Rates of Visits to the Children's Hospital and Parenteral Ceftriaxone per Calendar Year

Year	Incidence Rate of Parenteral Ceftriaxone							
	Incidence Rate of Visits		per 1000 visits		per 1000 person-years		Total (n)	AOM (n)
	Total (n)	AOM (n)	Total (n)	AOM (n)	Total (n)	AOM (n)		
2008	197 (12,229)	69.0 (936)	80.8 (988)	185 (173)	15.9 (988)	12.8 (173)		
2009	199 (12,514)	72.0 (1,012)	74.8 (936)	192 (194)	14.9 (936)	13.8 (194)		
2010	181 (11,339)	64.2 (925)	81.0 (918)	253 (234)	14.6 (918)	16.2 (234)		
2011	201 (12,645)	60.8 (890)	63.8 (807)	178 (158)	12.8 (807)	10.8 (158)		
2012	215 (13,150)	58.4 (830)	52.5 (691)	163 (135)	11.3 (691)	9.5 (135)		
2013	221 (13,518)	55.2 (772)	54.7 (739)	105 (81)	12.1 (739)	5.8 (81)		
2014	216 (13,323)	52.0 (708)	48.9 (652)	76 (54)	10.6 (652)	4.0 (54)		
2015	235 (14,502)	55.1 (731)	56.7 (822)	89 (65)	13.3 (822)	4.9 (65)		

Incidence rate (IR) of total visits is given per 1000 person-years at risk of children <18 years of age in the Children's Hospital's referral region with the number of visits given within parentheses. When calculated for acute otitis media (AOM), the IR are given per 1000 person-years of children <4 years of age in the referral region. IR of parenteral ceftriaxone is given both per 1000 visits and 1000 person-years with the number of ceftriaxone treatment episodes given within parentheses.

**TABLE 2.** Incidence Rate and Incidence Rate Ratio of Ceftriaxone Treatment Episodes Between Vaccine Periods Stratified by Indication and Age

Disease	Age	Incidence Rate per 1000 Person-Years (n)		IRR (95% CI)	<i>P</i>
		Prevaccine	Postvaccine		
Otitis media	0–1	0.70 (11)	0.4 (6)	0.6 (0.18–1.77)	0.31
	1–2	16.1 (247)	7.06 (104)	0.44 (0.35–0.55)	<0.001*
	2–3	6.7 (99)	2.9 (44)	0.43 (0.29–0.62)	<0.001*
Pneumonia	3–4	0.77 (11)	0.59 (9)	0.76 (0.28–2.02)	0.54
	0–1	0.95 (15)	0.14 (2)	0.15 (0.02–0.63)	0.003*
	1–2	6.92 (106)	2.31 (34)	0.33 (0.22–0.5)	<0.001*
Other	2–3	6.2 (91)	2.2 (33)	0.35 (0.23–0.53)	<0.001*
	3–4	2.7 (39)	1.4 (21)	0.5 (0.28–0.87)	0.010*
	0–1	16.6 (261)	20.6 (295)	1.24 (1.05–1.47)	0.012*
	1–2	14.9 (228)	12.5 (184)	0.84 (0.69–1.02)	0.08
	2–3	12.8 (189)	9.13 (139)	0.71 (0.57–0.89)	0.002*
	3–4	8.59 (123)	7.61 (117)	0.89 (0.68–1.15)	0.35

Number of treatment episodes given within parentheses.

\**P* values for the  $\chi^2$  test of difference in proportion are shown and those with a significance level under 0.05 are marked with an asterisk.

2008, 0.9% in 2009, 2.3% in 2010, 8.6% in 2011, 38% in 2012, 68% in 2013, 93% in 2014 and 97% in 2015. A total of 97% of children born in Iceland in 2011 later received at least 2 doses of PHiD-CV10.

### Rate of AOM Visits to the Children's Hospital

Visits for distinct episodes of AOM decreased significantly after vaccination from an incidence rate of 47.5 per 1000 person-years in the prevaccine period to an incidence rate of 33.9 per 1000 person-years postvaccine. The effect of vaccine period varied significantly across age strata precluding Mantel-Haenzel adjustment. The crude overall IRR was 0.86 (95% CI: 0.81–0.91; *P* < 0.001). A significant decrease in visits was observed only in children 2–3 years of age (IRR 0.71; 95% CI: 0.63–0.80; *P* < 0.001. A nonsignificant trend toward a decrease was observed in other age strata. Children 0–1 and 3–4 years of age visited the Children's Hospital because of episodes of AOM for a total of only 481 and 396 times, respectively, over the study period.

### Rate of Ceftriaxone Treatment Episodes

Significantly fewer episodes of AOM were treated with ceftriaxone in the postvaccine period compared with those in the prevaccine period (Table 1). The effect was consistent across age strata with an overall Mantel-Haenzel adjusted IRR 0.45 (95% CI: 0.37–0.54; *P* < 0.001). During the entire study period, only 16 episodes of AOM in children 0–1 year of age, and 20 episodes in children 3–4 years of age, were treated with ceftriaxone. Age-specific incidence rates and incidence rate ratios are shown in Table 2. The relative risk of treatment with ceftriaxone if presenting to the Children's Hospital with AOM decreased significantly after vaccination. The effect was consistent across age strata with a Mantel-Haenzel adjusted relative risk ratio of 0.53 (95% CI: 0.44–0.63; *P* < 0.001).

Episodes of pneumonia treated with ceftriaxone also decreased overall, from 251 treatment episodes in the prevaccine period to 90 in the postvaccine period, with a Mantel-Haenzel adjusted IRR 0.36 (95% CI: 0.28–0.45; *P* < 0.001. This significant decrease was observed in all age strata. Ceftriaxone use for other indications in children <4 years of age did not decrease significantly, with an IRR of 0.92 (95% CI: 0.84–1.02; *P* = 0.13. Age-specific incidence rates and incidence rate ratios by indication for each vaccine period are shown in Table 2. Quarterly incidence of ceftriaxone treatment episodes by indication is shown in Figure 1.

### Ceftriaxone Regardless of Indication by Age Groups

An overall decrease in incidence rate of ceftriaxone use in children <18 years of age regardless of indication was noted at the Children's Hospital Iceland after PHiD-CV10 introduction, from 0.93 treatment episodes per 1000 person-years in the prevaccine period to 0.80 in the postvaccine period with a crude overall IRR 0.86 (95% CI: 0.81–0.91; *P* < 0.001). However, when analyzed by age group, this is exclusively because of a significant decrease in incidence rate of ceftriaxone use in children 0–3 years of age (IRR 0.73; 95% CI: 0.67–0.79; *P* < 0.001). Ceftriaxone use did not decrease significantly in other age groups, and there was a trend toward increasing use in children 12–17 years of age (Figure 2).

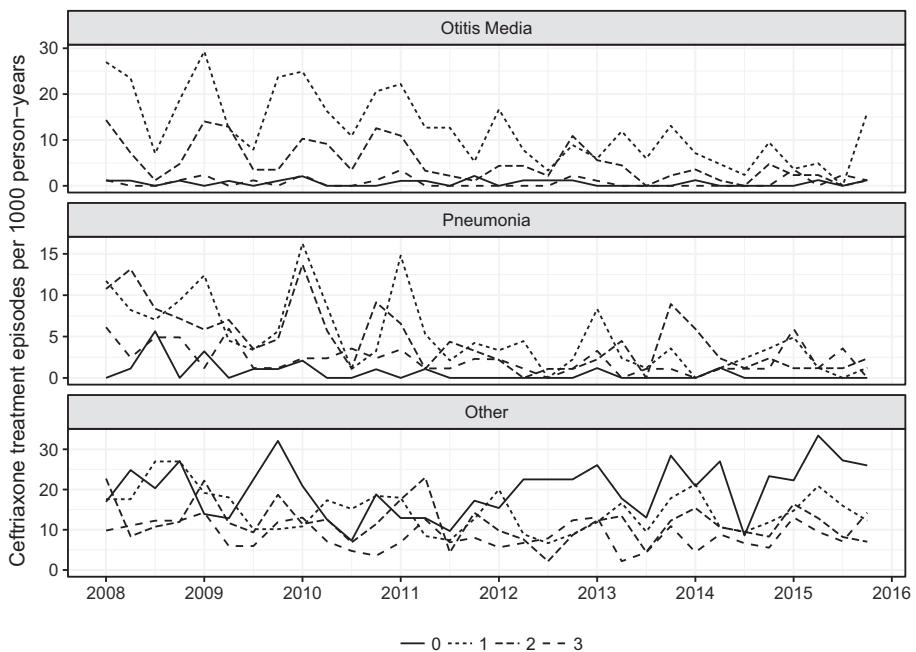
### DISCUSSION

In this study, we show a significant reduction in ceftriaxone use in the treatment of AOM at the Children's Hospital after introduction of PHiD-CV10 into the pediatric vaccination program in Iceland. When ceftriaxone is used in the treatment of AOM at the Children's Hospital, it is done exclusively in cases of treatment failure, difficult recurrent infections or in culture-proven antibiotic-resistant pneumococcus. The data suggest that this reduction is because of the effect of vaccination and is associated with a decrease in the prevalence of antibiotic-resistant pneumococcus. Before the introduction of PHiD-CV10, the proportion of PNSP isolates from middle ear was 48.7% of which 97.2% were serotypes covered by the vaccine.<sup>20</sup> Previous studies have shown a decrease in resistant clones of pneumococci after introduction of PCV.<sup>18,19</sup> This is mirrored in resistance rates published by the national reference laboratory at the Department of Clinical Microbiology, Landspítali University Hospital. Of all pneumococcal isolates collected in 2015, only 22% were PNSP.<sup>21</sup>

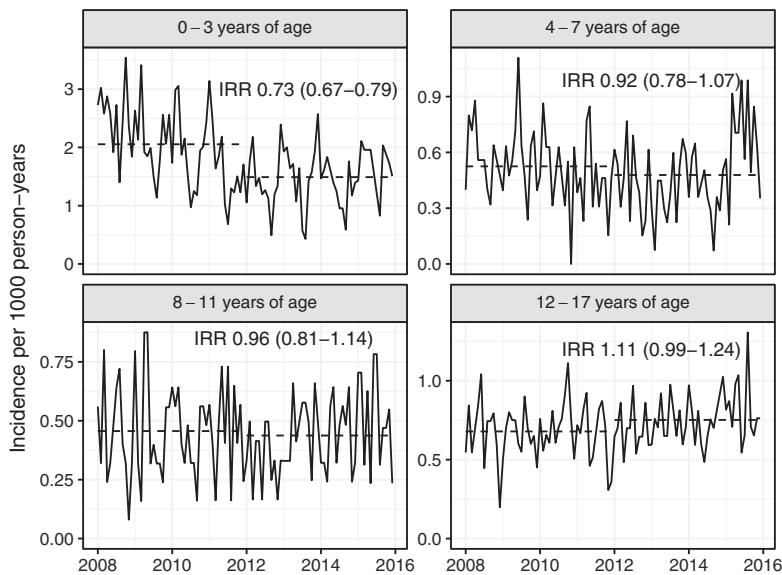
Because this is a retrospective observational study, causation between vaccine introduction and the observed decrease in AOM visits and ceftriaxone use cannot be directly inferred. However, this conclusion is supported by several observations. Ceftriaxone use decreased only for indications that would be expected if associated with the introduction of PHiD-CV10. We show that there was a significant decrease in the use of ceftriaxone to treat AOM and pneumonia in children 0–3 years of age. We did not observe a similar significant decrease in ceftriaxone use for other diagnoses, although there was a trend toward decrease. Ceftriaxone is the empiric treatment of choice for septic infants in the Children's Hospital Iceland. Therefore, the observed decrease in ceftriaxone use for other diagnoses may represent a decrease in the number of children with symptoms of sepsis who visited the Children's Hospital.

No changes in institutional guidelines regarding the treatment of AOM with treatment failure or use of ceftriaxone were introduced during the study period. We tested whether significant change had occurred in ceftriaxone use by age group and found a significant decrease only in the youngest children 0–3 years of age. The rate of ceftriaxone use regardless of indication remained unchanged in children 4–7, 8–11 and 12–17 years of age. This supports the hypothesis that the observed decrease is associated with PHiD-CV10 and is not because of an independent shift in hospital practices.

The Children's Hospital is Iceland's only pediatric referral hospital and also functions as a walk-in clinic for the capital area. To our knowledge, no change in guidelines or practices regarding referrals to the Children's Hospital occurred that could explain the observed decrease in AOM visits and ceftriaxone treatment. Even if this was the case, increased outpatient treatment of pediatric disease would likely cause an overall decrease in visits to the Children's



**FIGURE 1.** Incidence rate of ceftriaxone treatment episodes by year quarter. Different indications are represented with individual facets. Age is represented with different line types and specified in the legend below.



**FIGURE 2.** Incidence rate of ceftriaxone treatment episodes regardless of indication by year quarter. Age groups are represented with different facets. Incidence rate ratios (IRR) between pre- and postvaccine periods are given within each facet. Wald confidence intervals are shown within parentheses.

Hospital and a higher proportion of complex cases. This would be expected to cause an increase in the relative use of ceftriaxone for AOM. In contrast, we show that there was steady increase in the total number of visits to the Children's Hospital over the study period, but both an absolute and relative decrease in the number of visits for AOM. Similar findings have previously been published by our research group.<sup>22</sup> The observed reduction in ceftriaxone use for AOM remains significant after correcting for an observed decrease in AOM visits. Regrettably we do not have concurrent data on pneumonia-related hospital visits and are, therefore, unable to evaluate the relationship between decreased ceftriaxone treatment episodes and pneumonia cases. Nevertheless, in previous studies, pneumonia-related visits to the Children's Hospital by children under 2 years of age were shown to have decreased from 42.2 to 32.9 visits per 1000 person-years in the 2-year period before and pursuant to the vaccination.<sup>22</sup>

Randomized controlled trials (RCT) have shown mixed results regarding the protective effect of PCV against AOM, with effect sizes ranging from 7.8% (95% CI: 5.4%–10.2%),<sup>23</sup> 6% (95% CI: −4% to 16%),<sup>24</sup> 17% (95% CI: −2% to 33%),<sup>25</sup> and 0.4% (95% CI: −19.4 to −15.6%).<sup>26</sup> These studies evaluated the 7-valent PCV. However, 3 RCTs have studied the effect of a higher valent vaccine conjugate with *H. influenzae* protein D and found a reduction in all-cause AOM by 16.1% (95% CI: −1.1% to 30.4%).<sup>27</sup> 24% (95% CI: 8.7%–36.7%)<sup>28</sup> and 33.6% (95% CI: 20.8%–44.3%).<sup>29</sup> Furthermore, observational studies have consistently shown a larger effect size when compared with RCTs, which is hypothesized to be caused by indirect herd effect among the nonvaccinated.<sup>3,30–32</sup>

The study is strengthened by its long observation period. AOM visits and ceftriaxone use for AOM remained largely unchanged in the 4 years before vaccine introduction. Furthermore, there was immediate high vaccine uptake after introduction and a clear contrast in vaccination rates between the pre- and postvaccine periods. This increases our confidence in the relationship between vaccine introduction and the observed decrease. Data were complete over the study period and were systematically collected using unique personal identification numbers. Drug administration at the Children's Hospital was systematically documented with standardized procedural codes that did not change during the study period. This enabled us to retrieve exact data on AOM and ceftriaxone treatment on all individuals. The observation that ceftriaxone use for other indications did not change significantly between vaccine periods is consistent with our expectations, as ceftriaxone remains the empirical treatment of choice for severe infections at the Children's Hospital.

To our knowledge, this is the first study to show a significant decrease in AOM with treatment failure. AOM with treatment failure is not exactly defined in the literature. Proxy measurements are therefore needed. Ceftriaxone is avoided unless absolutely required and is not administered at primary care clinics. It is therefore an appropriate and clinically relevant end point, with regards to the worst cases of AOM with treatment failure. Proportion of PNSP decreased after vaccine introduction. However, these rates are also influenced by the rate at which physicians take samples for culture, which has been decreasing year by year from 2007 in Iceland. Our study mitigates such bias by measuring the treatment of AOM with treatment failure, most often because of resistant infections. There is, therefore, strong reason to believe a priori that PHiD-CV10 would lead to a reduction of AOM with treatment failure. The number of episodes of AOM treated with ceftriaxone in Iceland has decreased after introduction of PHiD-CV10 into the pediatric vaccination program. Visits to the Children's Hospital because of AOM have also decreased. The results strongly suggest a decrease in serious AOM with treatment failure because of antibiotic-resistant pneumococcus after vaccination.

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## **Paper II**



# Reduction in All-Cause Acute Otitis Media in Children <3 Years of Age in Primary Care Following Vaccination With 10-Valent Pneumococcal *Haemophilus influenzae* Protein-D Conjugate Vaccine: A Whole-Population Study

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**Background.** The 10-valent pneumococcal conjugate vaccine (PHiD-CV10) was introduced in Iceland in 2011, without catch-up. The aim of this study was to estimate vaccine impact (VI) on acute otitis media (AOM).

**Methods.** In this whole-population study, all primary care visits due to AOM from 2005 to 2015 in children <3 years of age were included. Birth cohorts were grouped as vaccine noneligible (VNEC) or vaccine eligible (VEC). Crude incidence rates (IRs) were compared between the VNEC and VEC. A Cox regression model for repeated events was used to model the individual-level data. VI was calculated as (hazard ratio [HR] – 1) × 100%.

**Results.** Included were 53 150 children, with 140 912 person-years of follow-up and 58 794 AOM episodes. Both IR and the mean number of episodes differed significantly between VNEC and VEC; 43 compared to 38 episodes per 100 person-years and 1.61 episodes per child compared to 1.37. IR was significantly reduced in all age brackets, with the largest reduction in children <4 months of age (40% [95% confidence interval {CI}, 31%–49%]). The VI on all-cause AOM was 22% (95% CI, 12%–31%). The impact was mediated through its effect on the first (HR, 0.84 [95% CI, .82–.86]) and second (HR, 0.95 [95% CI, .93–.98]) episodes.

**Conclusions.** The impact of PHiD-CV10 on all-cause AOM was considerable, mediated mainly by preventing the first two episodes of AOM. A decrease in the IR of AOM in children too young to receive direct vaccine protection was demonstrated, suggesting herd effect.

**Keywords.** pneumococcal vaccination; vaccine impact; acute otitis media; PCV-10; herd effect.

Acute otitis media (AOM) is one of the most common infectious diseases in children. It is estimated to have a global incidence rate of 61 episodes per 100 person-years (PY) in children 1–4 years of age, representing >700 million cases and resulting in 21 thousand deaths annually [1]. The incidence rate of AOM is lowest in Europe [1–3] but higher in the United States [4, 5], Iceland [6] and in developing countries [1].

Prior to the general introduction of pneumococcal conjugate vaccines (PCVs), the proportion of children who were diagnosed with AOM at least once before 3 years of age was estimated to be 80% [7]. In a post-PCV era prospective study conducted in the United States, 23%, 42%, and 60% of children were diagnosed with AOM by their first, second, and third birthday, respectively [8].

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*Streptococcus pneumoniae* and nontypeable *Haemophilus influenzae* (NTHi) are the most common bacterial causes of AOM [8–14]. Pneumococci are the major bacterial pathogen in early AOM. With each subsequent infection, the ensuing disruption of the middle ear increases the risk of complex, polymicrobial disease, in which NTHi is a common pathogen [13, 14]. Preventing early pneumococcal AOM may thereby prevent subsequent nonpneumococcal AOM [13].

PCV reduces the rate of both pneumococcal [15–19] and all-cause AOM [17, 18, 20] in randomized controlled trials (RCTs). Several postmarketing observational studies have demonstrated the impact of PCV on the incidence of pneumococcal, NTHi [21], and all-cause otitis media (OM) and AOM [22–25], as well as complex OM and tympanic tube placements [4, 26].

The 10-valent pneumococcal *Haemophilus influenzae* protein-D conjugate vaccine (PHiD-CV10, Synflorix, Belgium) was introduced into the routine childhood vaccination program in Iceland in April 2011, with a 2 + 1 schedule given at 3, 5, and 12 months of age. Children born 2011 and later were eligible to receive the vaccine. A catch-up schedule was not implemented. The vaccine uptake in Iceland was immediately high, with >97% of each vaccine-eligible birth cohort receiving ≥2 doses as of 2015 [27].

The aim of this whole-population study was to evaluate the vaccine impact of PHID-CV10 on all-cause AOM in children <3 years of age in Iceland.

## MATERIALS AND METHODS

### Data Sources

This is a whole-population, individual-level, observational cohort study of primary care visits due to AOM in children <3 years of age. The study encompasses the period between 1 January 2005 and 31 December 2015. All children born in Iceland in 2005 through 2015 were included and followed until 3 years of age, or until the end of the study period. A visit was defined to be due to AOM if an *International Classification of Diseases, Tenth Revision (ICD-10)* diagnostic code of suppurative otitis media (H66) was recorded by a physician. Repeated visits within 30 days from the initial visit were considered to be the same episode and excluded from the analysis.

Information on visits was extracted from the primary health-care database of the Icelandic Directorate of Health, which includes all 69 primary care health clinics in Iceland. Private pediatric clinics were not included due to coding differences. Data included all *ICD-10* codes linked to the visit as well as demographic information. Children were identified using their unique government-issued national identification numbers, which enabled tracking both chronologically and by primary care location. Temporary residents and travelers without national identification numbers were excluded to remove possible bias due to the increase in tourism in Iceland over the study period. Population demographic information was obtained from Statistics Iceland ([www.statice.is](http://www.statice.is)).

### Statistical Methods

Analyses were performed either on individual birth cohorts or on grouped cohorts based on vaccine eligibility. Birth cohorts 2005–2010 were grouped as vaccine noneligible (VNEC) and birth cohorts 2011–2015 as vaccine eligible (VEC). Statistical analysis was performed in R version 3.3.2 software using the survival package [28].

### Crude Incidence Rate and Cumulative Incidence

Crude incidence rates (IRs) were calculated per 100 PY at risk for each birth cohort, stratified by 4-month age brackets. Crude incidence rate ratios (IRRs) between VNEC and VEC were also calculated, and confidence intervals (CIs) estimated assuming the Poisson distribution. The cumulative incidence of children experiencing 0–12 episodes of AOM before 3 years of age was calculated and compared using the  $\chi^2$  test of homogeneity. Because birth cohorts 2013–2015 did not have complete follow-up time at the time of writing, they were excluded from the analysis of cumulative incidence. Additionally, the crude incidence risk ratio of experiencing 0, 1–4, or >5 episodes of AOM before 3 years of age was

calculated, and CIs adjusted for multiple testing using the Bonferroni correction.

### Regression Analysis

The Andersen-Gill extension of the Cox regression model for repeated events [29] was used to model the data on the individual level and to account for censoring of follow-up time. Sandwich variance estimates were used to correct for correlation between successive visits by the same individual.

The model was used to estimate the hazard ratio (HR) of AOM visits of each birth cohort compared to the last vaccine-noneligible cohort (2010 cohort, reference cohort), correcting for both gender and the number of previous AOM episodes. The overall vaccine impact of PHID-CV10 on AOM was calculated using  $1 - (\text{HR between the last included vaccine-eligible birth cohort [2015 cohort] and the reference cohort}) \times 100\%$ .

To characterize the mechanism by which the vaccine reduces the risk of AOM, the HR between VNEC and VEC was calculated, stratified by the number of previous AOM episodes.

Finally, the mean number of AOM episodes by age for both VNEC and VEC was calculated from the model using the generalized Nelson-Aalen estimator [29]. The absolute number of AOM episodes prevented by the vaccination in the first 5 years of the intervention was determined by multiplying each child's follow-up time by the corresponding mean number of episodes. The absolute IR reduction was then calculated by dividing the number of prevented episodes with the total person-time of the VEC.

The study was approved by the National Bioethics Committee (VSNB2013010015/03.07.95) and the National Data Protection Authority (2013010100VEL/-).

## RESULTS

The study included 53 150 children who contributed 140 912 PY of follow-up time. A total of 74 802 visits for AOM were recorded, of which 16 008 were repeated visits within 30 days. After the exclusion of repeated visits, 58 794 episodes of AOM remained.

### Crude Incidence Rate and Cumulative Incidence

The overall crude IR of AOM for the whole study period was 41.7 per 100 PY; 43.6 in the VNEC and 38.0 in the VEC. The IRs for the first, second, and third year of life for the VNEC and VEC are shown in Table 1. The IR was lowest in children <4 months of age, and highest in children 8–11 and 12–15 months of age. It decreased significantly in all age brackets following vaccination (Figure 1). The largest decrease was noted in children <4 months of age (40% [95% CI, 31%–49%]), from 5.60 to 3.33 cases per 100 PY. In other age brackets, the decrease was 6%–23% (Figure 1).

The cumulative incidence of AOM episodes between VNEC and VEC differed significantly ( $\chi^2$  test 56.1,  $P < .001$ ).

**Table 1.** Incidence Rate per 100 Person-years and Acute Otitis Media Episodes for the Vaccine-Noneligible and Vaccine-Eligible Cohorts, by Age

Cohort	Age Group, y	IR (No. of AOM Episodes)	Total Person-years at Risk
VNEC	<1	48.3 (13474)	30436
	1 to <2	57.2 (17419)	30436
	2 to <3	29.1 (8872)	30436
VEC	<1	34.2 (7232)	21150
	1 to <2	51.9 (8692)	16750
	2 to <3	25.5 (3105)	12199

Abbreviations: AOM, acute otitis media; IR, incidence rate; VEC, vaccine-eligible cohort; VNEC, vaccine-noneligible cohort.

The proportion of children who experienced >5 episodes of AOM decreased, with a corresponding increase in children who did not experience a single episode of AOM. The incidence proportion and crude incidence risk ratio of experiencing 0, 1–4, and >5 episodes of AOM are shown in **Table 2**.

#### Regression Analysis

Model diagnostic testing did not reveal significant deviations from the model assumptions. The hazard of contracting a new episode of AOM increased with each consecutive episode. The hazard of AOM varied little between the VNEC birth cohorts. Only the 2007 cohort differed significantly compared to the reference cohort (HR, 1.07 [95% CI, 1.02–1.12]). Conversely, the hazard of AOM in each of the vaccine-eligible birth cohorts decreased significantly compared to the reference cohort, with HRs ranging from 0.78 to 0.89 (**Figure 2**). The estimated vaccine impact of PHiD-CV10 on all-cause AOM was 22% (95% CI, 12%–31%).

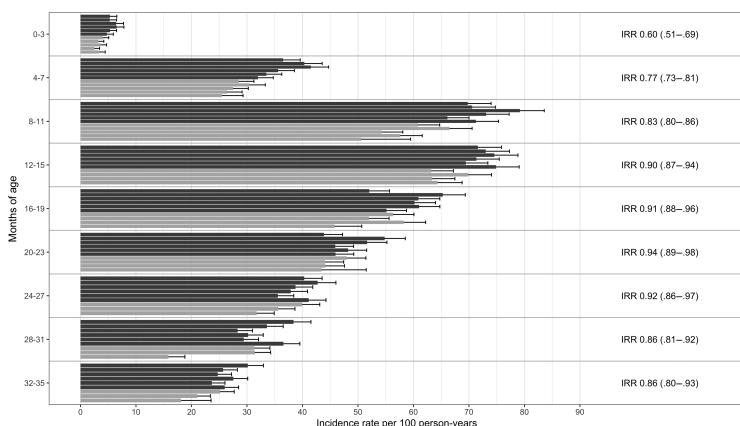
When stratified by the number of previous AOM episodes, the vaccination showed a significant impact in preventing both the first episode (HR, 0.84 [95% CI, .82–.86]) and the second episode (HR, 0.95 [95% CI, .93–.98]) of AOM. No significant

impact was noted on the hazard of experiencing subsequent AOM episodes after the third one.

By 3 years of age, the mean number of AOM episodes per child in the VNEC and VEC was 1.61 and 1.37, respectively. The mean number of episodes from birth to 3 years of age is displayed in **Figure 3**. The difference in the mean number of episodes between VNEC and VEC was significant from birth, and increased as the child aged. The absolute number of prevented episodes of AOM in children <3 years of age in the first 5 years of the intervention was 4187 (95% CI, 3363–5011), and the absolute IR reduction was 8.4 episodes per 100 PY (95% CI, 6.78–10.1).

#### DISCUSSION

In this whole-population study, we have demonstrated a 22% vaccine impact of PHiD-CV10 on all-cause AOM. The vaccine is associated with a significant reduction in the first and second episodes of AOM, but does not prevent further episodes in those who have already experienced ≥2 episodes. There were significant reductions in the crude IR of AOM in all age brackets, including a 40% (95% CI, 31%–49%) reduction in children



**Figure 1.** Incidence rates per 100 person-years with 95% confidence intervals are shown for each study birth cohort by 4-month age bracket. The vaccine-noneligible cohorts are colored dark gray and the vaccine-eligible cohorts light gray. Abbreviation: IRR, incidence rate ratio.

**Table 2.** Incidence Proportion of the Number of Acute Otitis Media Episodes for the Vaccine-Noneligible and Vaccine-Eligible Cohorts, With Incidence Risk Ratio

No. of AOM Episodes	Incidence Proportion, % (No.)		Incidence Risk Ratio (98.3% CI <sup>a</sup> )
	VNEC	VEC	
0	40.3% (12267)	43.6% (4329)	1.08 (1.05–1.12)
1–4	55.5% (16886)	52.9% (5143)	0.95 (.93–.98)
>5	4.2% (1283)	3.6% (346)	0.84 (.73–.97)

Abbreviations: AOM, acute otitis media; CI, confidence interval; VEC, vaccine-eligible cohort; VNEC, vaccine-noneligible cohort.

<sup>a</sup>Bonferroni-adjusted CI for the incidence risk ratio.

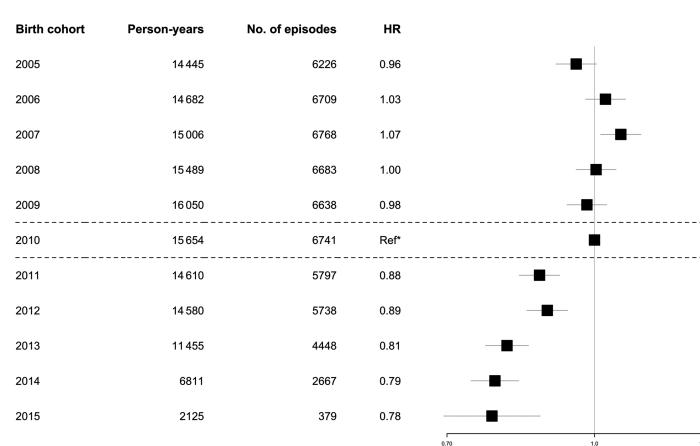
too young to receive direct vaccine protection. This suggests that herd protection was induced by the vaccination.

The present study is strengthened by several factors. It follows 11 consecutive birth cohorts until 3 years of age through a whole-country population registry of primary care visits, using a broad definition of AOM. Generally, RCTs evaluating the efficacy of PCV against AOM report larger effect sizes than the more restrictive their outcome measure. RCTs have reported larger vaccine efficacy (57%–70%) [15, 17–19] against vaccine-type pneumococcal AOM than against pneumococcal AOM (34%–56%) [16, 18]. The efficacy estimates against all-cause AOM are less still, from 8% to 34% [17, 18, 20]. When evaluating the outcome measure of all-cause AOM, many RCTs use more stringent diagnostic criteria than is generally adhered to in the community setting, often employing certified otoscopists to diagnose what general physicians normally do. Though more accurate, these studies are inadequate when informing public policy or determining cost-effectiveness. Observational studies have shown a larger impact of PCV on all-cause OM, with vaccine impact estimates of from 14% to 57% [22, 24, 25]. However, these studies may be biased due to case ascertainment

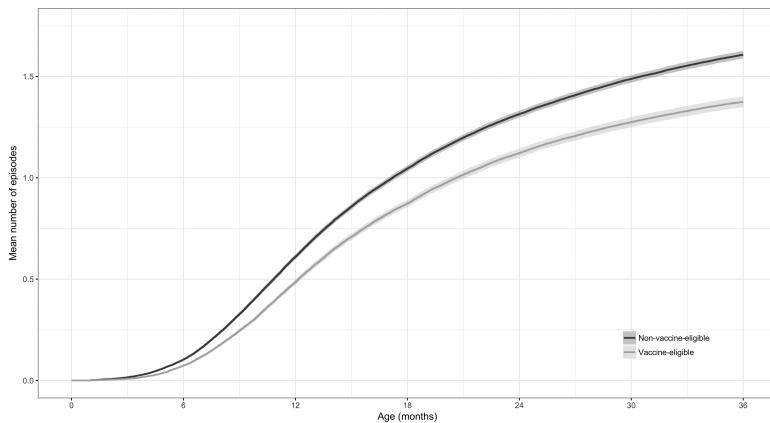
and unclear study populations. Our study addresses the least restrictive definition of AOM—all-cause, physician-diagnosed AOM—and its study population contains all children <3 years of age in Iceland, with no known exceptions.

Another strength of this study is the individual based nature of the data, which allows for data collection on a single child through multiple visits regardless of location or time. This permits the use of sophisticated survival analysis methods normally reserved for experimental studies. Using these methods, the correlation between successive AOM episodes can be taken into account, an analysis which is unfeasible in conventional observational studies.

We show that PHiD-CV10 reduces the incidence of AOM through its impact on the first and second episodes of AOM. No independent effect was noted on subsequent AOM episodes in those who had already experienced ≥2 episodes. *Streptococcus pneumoniae* is adept in causing AOM in previously healthy middle ears and is often the cause of a child's first episode [13, 14]. This initial AOM episode is believed to cause injury to the middle ear, making it susceptible to AOM by other, less virulent pathogens. The observed independent protection of



**Figure 2.** Hazard ratios (HRs) along with 95% confidence intervals for each of the study birth cohorts compared to the last vaccine-noneligible birth cohort (2010) are shown. The figure includes the total number of person-years and number of acute otitis media episodes experienced by each birth cohort. The HR point estimate between each of the study birth cohorts and the 2010 cohort are also shown. \*Ref, reference birth cohort.



**Figure 3.** The mean number of acute otitis media episodes for children 0–36 months of age. The 95% confidence intervals are shown with shaded areas. The vaccine-non-eligible cohorts are colored dark gray and the vaccine-eligible cohorts light gray.

PHiD-CV10 against the first and second AOM episode, and not subsequent episodes, may therefore be explained by the middle ear injury incurred by initial pneumococcal AOM. This in turn induces susceptibility to other pathogens, against which PHiD-CV10 offers no protection.

The proportion of children in the VEC who have never experienced an episode of AOM by 3 years of age is significantly higher than those in the VNEC (IRR: 1.08 [98.3% CI, 1.05–1.12]). We also show the mean number of AOM episodes as a function of age for both the vaccine-noneligible and vaccine-eligible cohorts, and use this to estimate the absolute number of averted episodes of AOM. On average, each episode of AOM resulted in 1.26 physician visits within 30 days. As repeated visits within 30 days were excluded from the analysis, the actual number of averted physician visits is considerably higher than reported here.

The reported crude incidence of AOM varies up to 10-fold between studies in different countries and settings [24]. There are several possible cultural and economic reasons for this variance. Factors such as access to and cost of healthcare can mean portions of populations delay or eschew physician visits for mild disease [30, 31]. This is not the case in Iceland, where healthcare is guaranteed for all permanent residents, access to urgent care is excellent, and primary care for children is free of charge. These advantages, combined with the fact that generally both parents are fully employed and enrollment of Icelandic children in daycare is high, may increase the likelihood of early medical intervention for mild disease. The Organisation for Economic Co-operation and Development (OECD) ranks Iceland second in formal daycare attendance with up to 60% of children <3 years of age attending for 38 hours per week, compared to the OECD average of 35% attendance for 30 hours [32]. Both

attendance and hours per week are known risk factors for AOM [33, 34]. Finally, the pneumococcal carriage rate is also higher in Iceland than in most developed countries [35]. Reflecting these cultural and economic differences, the crude postvaccination incidence rate reported in this study, 30.0 per 100 PY, is lower than previously reported incidence from Iceland (63–70 per 100 PY) [6] and the United States and Canada (42–122 per 100 PY) [4, 5, 8], but higher than in other European countries and in New Zealand (16–33 per 100 PY) [2, 3, 36, 37].

In addition to the reduction in IR noted in all age brackets of vaccinated children, we also observed a significant 40% reduction in the IR of AOM in children <4 months of age following vaccine introduction. This provides evidence for a herd effect, as children in this age group are too young to have direct protection from the vaccination [38]. There is a paucity of published data regarding herd effect of PCV against AOM [19, 39]. A recent study reported fewer positive pneumococcal cultures from middle ear fluid samples in children <4 months of age after the introduction of PCV, suggesting a possible herd effect [21]. The results of our study strengthen that earlier suggestion.

Several factors must be considered when interpreting the study results. First, the impact of vaccination status was not modeled directly; rather, the vaccine eligibility of birth cohorts was used as a proxy for vaccination status. We argue that there is strong evidence for the validity of this proxy measure, as <1% of children in the early VNECs were vaccinated compared with >97% of children in the VECs [27]. The proportion of vaccinated children was slightly higher in the last 2 VNECs, with 9% of children in the 2009 cohort and 19% in the 2010 cohort vaccinated. This increase may be due to heightened interest in pneumococcal vaccination as its inclusion into the pediatric vaccination program in Iceland in 2011 was imminent. In any

case, this would likely bias the vaccine impact estimate downward, if at all, as the 2010 cohort was used as the reference.

Second, due to the observational nature of the study, it is not possible to exclude the possibility that coding practices or healthcare-seeking behavior might have changed during the study period. Reductions in AOM diagnoses have been reported worldwide since the millennium [24]. This gives reason to suspect that some of study's observed effect may be due to secular trends. However, this does not seem to be supported by the data. The study's results are summarized in Figures 1 and 2, showing, respectively, the crude incidence and hazard of AOM episodes by birth cohort. When each birth cohort is compared to the last VNEC (2010) using the individual data corrected for gender and censored observations, it becomes clear that there exists little variation in the hazard of AOM between individual noneligible birth cohorts. Only the 2007 birth cohort is significantly different from the 2010 cohort, and there is even less difference between proximal cohorts. In contrast, there is an abrupt drop in the hazard of AOM in the first vaccine-eligible birth cohort (2011) compared to 2010, and the hazard of each VEC is significantly decreased. In 2009, updated guidelines on AOM were published by the Icelandic Directorate of Health [40]. After these guidelines were issued, it is possible that AOM diagnoses became more restricted. This hypothesis, however, is not supported by our data. The hazard of AOM in the 2009 and 2010 birth cohorts is not significantly different than the other VNECs. Furthermore, as the 2010 cohort was used as a reference in calculating the vaccine impact estimate, the guidelines cannot be considered a confounder. An increase in private physician visits could present another potential bias, as private visits could not be included in the study due to differences in diagnostic coding. However, this is unlikely to be significant. Although information from Statistics Iceland (<http://statice.is/statistics/society/health/healthcare>) shows an increasing number of total visits to private pediatricians in recent years, the number of after-hours and emergency visits has remained stable at around 11 000 visits each year for children <18 years of age (personal correspondence with head of the only after-hours/emergency pediatric clinic). This indicates that the increase is due to planned nonemergency visits rather than emergency ones, such as AOM.

## CONCLUSIONS

This study, which follows 11 consecutive Icelandic birth cohorts (2005–2015) up to 3 years of age, demonstrates a 22% vaccine impact of PHiD-CV10 on all-cause AOM, and provides evidence of herd effect against AOM in children too young to receive direct protection. The impact is shown to be mediated through an independent effect on the first and second episodes of AOM, but no significant effect is noted for subsequent episodes.

## Notes

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## **Paper III**



RESEARCH ARTICLE

Open Access



# Impact of the 10-valent pneumococcal conjugate vaccine on antimicrobial prescriptions in young children: a whole population study

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## Abstract

**Background:** Antimicrobial resistance is a public-health threat and antimicrobial consumption is the main contributor. The ten-valent pneumococcal conjugate vaccine (PHiD-CV10) was introduced into the Icelandic vaccination program in 2011.

The aim was to estimate the vaccine impact of PHiD-CV10 on outpatient antimicrobial prescriptions in children.

**Methods:** Eleven Icelandic birth-cohorts (2005–2015) were followed from birth until three years of age or to the end of the study period (December 31, 2016). Birth-cohorts were grouped as vaccine non-eligible (VNEC, 2005–2010) or vaccine eligible (VEC, 2011–2015). Data on primary care visits for respiratory infections and antimicrobial prescriptions were extracted from two national registers. Using national identification numbers, prescriptions were linked to physician visits if filled within three days of the visit. Incidence rates and incidence rate ratios between VNEC and VEC were calculated. An Andersen-Gill model was used to model the individual level data, accounting for repeated events and censoring. Vaccine impact was calculated as  $(1 - \text{Hazard Ratio}) \times 100\%$ .

**Results:** Included were 53,510 children who contributed 151,992 person-years of follow-up and filled 231,660 antimicrobial prescriptions. The incidence rate was significantly lower in the VEC compared to the VNEC, 144.5 and 157.2 prescriptions per 100 person-years respectively (IRR 0.92, 95%CI 0.91–0.93). Children in VEC were more likely to have filled zero (IRR 1.16 (95%CI 1.10–1.23) and 1–4 (IRR 1.08 95%CI 1.06–1.11) prescriptions compared to children in VNEC. The vaccine impact of PHiD-CV10 against all-cause antimicrobial prescriptions was 5.8% (95%CI 1.6–9.8%). When only considering acute otitis media-associated prescriptions, the vaccine impact was 21.8% (95%CI 11.5–30.9%).

**Conclusion:** The introduction of PHiD-CV10 lead to reduced antimicrobial use in children, mainly by reducing acute otitis media episodes. This intervention therefore reduces both disease burden and could slow the spread of antimicrobial resistance.

**Keywords:** Pneumococcal vaccines, Antibiotic agents, Otitis media, Observational study, Survival analysis

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## Background

Acute otitis media (AOM) and other upper respiratory tract infections (URTI) are the most common causes of ambulatory physician visits and antimicrobial prescriptions in children [1, 2]. The most common bacterial causes of URTI in young children are *Streptococcus pneumoniae* and *Haemophilus influenzae*, though most are caused by viral pathogens [3–6]. Distinguishing between viral and bacterial URTI can be difficult. As much as 30–50% of outpatient antimicrobial prescriptions for URTI are inappropriate [2, 7, 8]. Physicians cite the uncertainty of diagnosis and fear of disease complications as two important factors contributing to inappropriate prescriptions [2, 9–11], which in turn increases antimicrobial resistance [12, 13].

Antimicrobials were once universally recommended in the treatment of AOM to prevent complications. However, when several studies showed no increase in complications in populations with lower prescription rates [2, 14], this endorsement came under scrutiny. As a result, guidelines which recommended more restrictive prescription practices to combat rising antimicrobial resistance were adopted in many countries in the early 2000s [14–17]. This has led to a subsequent decrease in antimicrobial consumption [14, 16, 18, 19].

Concurrently, pneumococcal conjugate vaccines (PCV) were widely introduced into paediatric vaccination programs and have been associated with a decrease in AOM incidence [1, 18, 20–23]. Several randomized controlled trials (RCT) of PCVs have also shown a decrease in both all-cause and URTI-associated antimicrobial prescription rates [24–26].

The 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV10, Synflorix™) was introduced into the Icelandic paediatric vaccination program, with a 2 + 1 schedule without a catch-up for all children born in 2011 and later. Following the introduction, over 97% of each vaccine eligible birth-cohort received ≥2 doses of the vaccine [27]. Prior to the introduction of PHiD-CV10, few children were vaccinated, 0–1.9% of birth-cohorts, while 6.9% and 18.7% of children in birth-cohorts 2009 and 2010 received ≥2 doses [27].

The aim of this study was to investigate the impact of PHiD-CV10 against outpatient antimicrobial prescriptions for children < 3 years of age in Iceland.

## Methods

### Data sources

The study is a whole population observational cohort study of all children under three years of age in Iceland. Eleven consecutive birth-cohorts 2005–2015 were followed until three years of age or to the end of the study period, December 31, 2016. Individual level data on

immigration and emigration was obtained from Statistics Iceland. Children who immigrated to Iceland after birth were excluded from the analysis. Observations were censored on death or emigration from Iceland. The 2016 birth-cohort was not included due to short follow-up time.

Data on outpatient antimicrobial prescriptions was extracted from the National Prescription Database (NPD) of the Directorate of Health. The NPD receives automated electronic data from all pharmacies in Iceland, and registers detailed information on each outpatient prescription in the country, identifiable down to the individual and day of purchase. All drug prescriptions with the anatomical therapeutic chemical (ATC) classification code J01 (antibacterials for systemic use) and subgroups were extracted from the NPD.

Information regarding primary care visits for respiratory tract infections was obtained from the Primary Care Database of the Directorate of Health. All visits with International Classification of Diseases, 10th Revision (ICD-10) discharge diagnoses compatible with respiratory tract infections were extracted as previously described [23]. This data was linked to the NPD using national identification numbers. Prescriptions were paired with a physician visit if filled for the same child within three days of the visit. Data from the Primary Care Database was available only through December 31, 2015, restricting the use of linked data to that date. Information on population demographics was acquired from Statistics Iceland (<https://www.statice.is/>).

### Statistical analysis

The study analysis was done by comparing birth-cohorts individually or grouped by vaccine eligibility. Individual birth-cohorts were each compared to the last vaccine non-eligible birth-cohort (2010) which was used as a reference cohort. Birth-cohorts 2011–2015 were grouped as the vaccine-eligible cohorts (VEC) and birth-cohorts 2005–2010 as the vaccine non-eligible cohorts (VNEC).

Aggregate analyses by calendar year were performed for all children under three years of age. Antimicrobials were classified into six classes; first and second line penicillins, first and second generation macrolides, cephalosporins and others (Table 1) [28]. The proportion of antimicrobial prescriptions in each class was calculated by calendar year. Similarly, the proportion of primary care visits resulting in antimicrobial prescription in each calendar year was calculated by indication. Five groups were defined based on ICD-10 discharge diagnosis; Acute upper respiratory infections (J00–J06), Influenza and pneumonia (J09–J18), Other acute lower respiratory infections (J20–J22), AOM (H65, H66 and H72) and Other viral infections (B34).

**Table 1** Classification of antimicrobials used in this study

First-line penicillins	Amoxicillin, phenoxyethylpenicillin
Second-line penicillins	Amoxicillin and enzyme inhibitor
First-generation macrolide	Erythromycin
Second-generation macrolide	Azithromycin, clarithromycin,
Cephalosporin	Cefalexin
Others	Ciprofloxacin, clindamycin, pivmecillinam, Trimethoprim/sulfmethoxazole,

### Crude incidence analysis

Incidence rates (IR) per 100 person-years at risk for each of the study birth-cohorts were calculated in six-month age-groups and 95% confidence intervals estimated using the Wald method. Incidence rate ratios (IRR) between the VNEC and the VEC were estimated and 95% confidence intervals calculated assuming Poisson variance.

The cumulative proportion of outpatient antimicrobial prescriptions by three years of age was compared between VNEC and VEC using the Chi-squared test of homogeneity. For this analysis, the 2014 and 2015-cohorts were excluded as they did not have the full three-year follow-up time. The cumulative number of outpatient antimicrobial prescriptions per child was stratified into brackets <1, 1–4, 5–9, 10–14 and ≥15 and the incidence risk ratio between VNEC and VEC was calculated for each bracket.

### Regression analysis

The Andersen-Gill extension of the Cox [29] regression model for repeated events was used to model the individual level data and allow for censored follow-up times. The model included age as the underlying measure of time to directly correct for age and was stratified allowing different baseline-hazards for each gender. The cumulative number of previous antimicrobial prescriptions was included as a covariate and modelled using a restricted cubic spline relationship. Finally, birth-cohort membership was included as a categorical variable. Robust sandwich variance estimates were included to account for correlation between successive observations of the same child. The model was used to estimate the hazard ratio (HR) of antimicrobial prescription between each of the study birth-cohorts and the reference birth-cohort. The vaccine impact of PHiD-CV10 in reducing outpatient antimicrobial prescriptions was then estimated as 1 – (the hazard ratio between the last vaccine eligible cohort and the reference cohort) × 100%.

The vaccine impact against each successive prescription was estimated by calculating the hazard ratio of antimicrobial prescription between VEC and VNEC for each number of previous prescriptions.

Finally, the mean number of antimicrobial prescriptions for each gender and vaccine-cohort was calculated

as a function of age using the generalized Nelson-Aalen estimate [29]. This was used to estimate the absolute number of prevented antimicrobial prescriptions during the first seven years of the intervention by adding together the expected number of prescriptions per child using the VNEC estimate of the mean and subtracting the expected number of prescriptions per child using the VEC estimate of the mean. The absolute rate reduction was calculated by dividing this estimate with the number of person-years at-risk in the VEC.

A sub-analysis was performed to estimate the vaccine impact against AOM-associated antimicrobial prescriptions. The same regression methodology was applied to a subset of the prescriptions which were linked to a primary care physician visit with a diagnosis of AOM. Vaccine impact was similarly estimated as 1 – (the hazard ratio between the last vaccine eligible cohort and the reference cohort) × 100%.

## Results

### Population

Information was available for 53,218 children born from 2005 to 2015. Children who immigrated to Iceland (1892) were excluded from the analysis. An additional 756 children were excluded due to lack of information on gender or date-of-birth. The remaining 50,570 children were followed for a total of 140,429 person-years and accumulated 226,181 antimicrobial prescriptions. Of the children who had a full three-year follow-up time, the median number of prescriptions per child was 4 prescriptions (IQR 2–7, range 0–55). Person-years at-risk by age-group for children in the VNEC and VEC is shown in Table 3.

### Antimicrobial usage

First-line penicillins were the most commonly prescribed antimicrobials in 2005–2012 and represented between 41 and 47% of all prescriptions. In 2013, their use decreased to 32% and in 2014 and 2015 to 18%. In 2016, it increased to 35%. Concurrently, the use of second-line penicillins increased from 35 to 40% in 2005–2012, to 48%, 55%, and 54% in 2013, 2014 and 2015 respectively, before decreasing to 42% in 2016. The use of cephalosporins was 5.2–7.8% in 2005–2012 and increased to 10–15% in 2013–2016. Use of macrolides and other antimicrobials can be seen in Table 2.

### Crude incidence rate and incidence rate ratios

The overall crude rate of antimicrobial prescriptions for children <3 years of age was significantly lower in the VEC than the VNEC, 150.3 and 167.6 antimicrobial prescriptions per 100 person-years respectively (IRR 0.90, 95%CI 0.89–0.91). The crude incidence per six-month age-groups are shown in Table 3. The crude incidence

**Table 2** Number of prescription per calendar year for children < 3 years of age and the proportion of each antimicrobial class

Calendar year	Incidence of prescriptions per 100 person-years (n)	First line penicillins (%)	Second line penicillins (%)	First generation macrolides (%)	Second generation macrolides (%)	Cephalosporins (%)	Other (%)
2005	204 (25649)	41.41	37.92	1.48	6.55	5.37	7.26
2006	205 (26396)	40.34	39.57	1.27	6.22	5.36	7.24
2007	192 (25179)	44.97	36.80	1.60	6.39	5.16	5.08
2008	178 (24046)	46.74	35.22	0.20	6.37	5.91	5.57
2009	159 (22406)	46.41	37.16	0.05	5.51	6.33	4.55
2010	167 (24007)	43.71	38.55	0.02	5.54	7.02	5.17
2011	164 (23866)	44.70	37.92	0.03	5.91	7.47	3.98
2012	160 (22703)	43.45	39.01	0.01	6.92	7.77	2.83
2013	152 (21113)	32.10	48.08	0.02	6.56	10.03	3.20
2014	152 (20325)	18.48	55.46	0.01	6.60	14.53	4.92
2015	150 (19873)	18.49	53.91	0.06	7.25	14.95	5.34
2016	160 (20543)	35.28	41.68	0.04	5.52	12.91	4.57

rate was highest among children 12–17 months of age in both VNEC and VEC, 247 and 233 prescriptions per 100 person-years respectively. The incidence rate of prescriptions decreased in all age-groups (IRR 0.82–0.94) with the largest decrease (IRR 0.82, 95%CI 0.79–0.85) in children < 6 months of age (Fig. 1).

The crude cumulative proportion of antimicrobial prescriptions at three years of age was 86.7% and 84.9% for the VEC and VNEC. A significantly larger proportion of children in the VEC had 0 or 1–4 prescriptions compared to children in the VNEC (incidence risk ratios 1.13, 95%CI 1.06–1.21 and 1.08, 95%CI 1.05–1.11 respectively). Concurrently, the proportion of children who filled ≥5 prescription decreased (Table 4).

The proportion of visits due to AOM which resulted in an antimicrobial prescription increased gradually 2005–2015 from 57 to 64% (Additional file 1: Figure S1). The incidence rate of AOM-associated prescriptions decreased from a high of 54.9 prescriptions per 100 person-years in 2008 to 39.8 prescriptions per 100 person-years in 2015. The crude incidence rates of

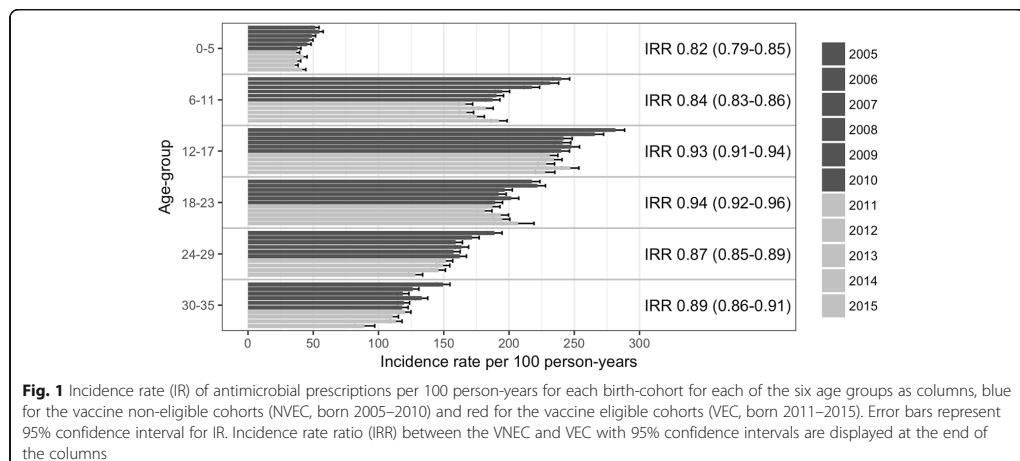
AOM-associated prescriptions by six-month age-groups are shown in Table 3. Concurrently, the proportion of AOM-associated antimicrobial prescriptions, out of all linked prescriptions remained stable between 59 and 66% (Fig. 2, Additional file 2: Table S1). Similarly, the incidence and proportion of visits due to acute upper respiratory infections which resulted in a antimicrobial prescription, increased from 2005 to 2008 after which it plateaued (Fig. 2 and Additional file 2: Table S1).

#### Individual level regression modelling of all-cause antimicrobial prescriptions

No significant deviation from model assumptions was noted in model diagnostic testing. The hazard of filling an antimicrobial prescription was significantly higher in the first three VNEC compared to the reference cohort (HR 1.08 95%CI 1.05–1.13, HR 1.12 95%CI 1.07–1.15) and HR 1.05 95%CI 1.01–1.09 respectively) while the hazard of birth-cohorts 2008 (HR 1.02 95%CI 0.98–1.06) and 2009 (HR:1.02 95%CI 0.98–1.06) did not differ from it significantly. Conversely, each vaccine-eligible birth-cohorts

**Table 3** Incidence rate (IR) of all-cause and AOM-associated antimicrobial prescriptions per 100 person-years, comparing the Vaccine non-eligible cohorts (born 2005–2010, VNEC) to the Vaccine eligible cohorts (born: 2011–2015, VEC). <sup>a</sup>Primary care data was only available until December 31st 2015. Therefore fewer person-years at-risk were available for the VEC when considering AOM-associated prescriptions and are as follows; 10,719; 9613; 8508; 7323; 6215 and 5083

Age-groups (months)	VNEC		Person-years at-risk	VEC		Person-years at-risk	
	IR (n of prescriptions)			IR (n of prescriptions)	Person-years at-risk		
	All cause	AOM-associated		All cause	AOM-associated		
< 6	47.0 (6816)	11.6 (1681)	14,491	39.1 (4338)	7.58 (813)	11,096 <sup>a</sup>	
6–11	206 (29,674)	69.1 (9931)	14,378	176 (19,447)	52.5 (5045)	11,024 <sup>a</sup>	
12–17	247 (35,226)	72.9 (10,372)	14,233	233 (24,588)	62.2 (5295)	10,566 <sup>a</sup>	
18–23	199 (28,008)	49.9 (7309)	14,096	189 (17,876)	46.6 (3411)	9460 <sup>a</sup>	
24–29	164 (22,843)	35.0 (4882)	13,965	144 (12,069)	30.3 (1882)	8374 <sup>a</sup>	
30–35	125 (17,259)	24.1 (3331)	13,848	112 (7218)	21.1 (1074)	7218 <sup>a</sup>	



**Fig. 1** Incidence rate (IR) of antimicrobial prescriptions per 100 person-years for each birth-cohort for each of the six age groups as columns, blue for the vaccine non-eligible cohorts (VNEC, born 2005–2010) and red for the vaccine eligible cohorts (VEC, born 2011–2015). Error bars represent 95% confidence interval for IR. Incidence rate ratio (IRR) between the VNEC and VEC with 95% confidence intervals are displayed at the end of the columns

exhibited significantly lower hazard as compared to the reference cohort, with hazard ratios ranging from 0.90–0.94 (Fig. 3). The estimated PHiD-CV10 vaccine impact against all-cause antimicrobial consumption was 5.8% (95%CI 1.6–9.8%).

The hazard of receiving an additional antimicrobial prescription increased with each prescription, with the steepest increase following the first three prescriptions. The vaccine was associated with a significantly lower hazard of filling the first (HR 0.88, 95%CI 0.87–0.90), second (0.94 HR 0.92–0.96) and third (HR 0.97, 95%CI 0.95–0.99) prescriptions, but no significant difference was noted in the hazard of filling subsequent prescriptions.

The mean number of prescriptions in the first three years of life is displayed in Fig. 4. At 36 months of age, the mean number of prescriptions decreased from 6.07 (95%CI 6.00–6.14) to 5.46 (95%CI 5.38–5.55) among girls

and from 6.48 (95%CI 6.42–6.55) to 5.84 (95%CI 5.76–5.93) among boys, in the VNEC and VEC respectively. The estimated absolute number of prevented prescriptions in the first six years of the intervention was 12,612 (95%CI 9471–15,752) with an absolute incidence rate reduction of 22.0 (95%CI 16.5–27.5) antimicrobial prescriptions per 100 person-years.

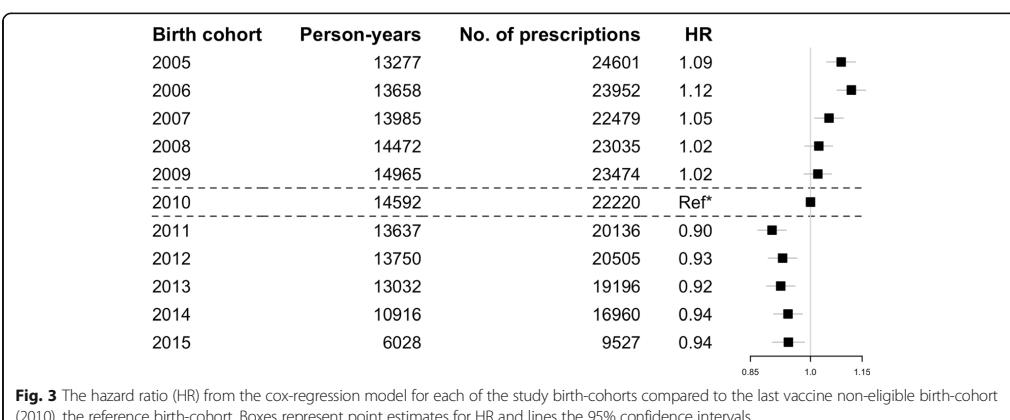
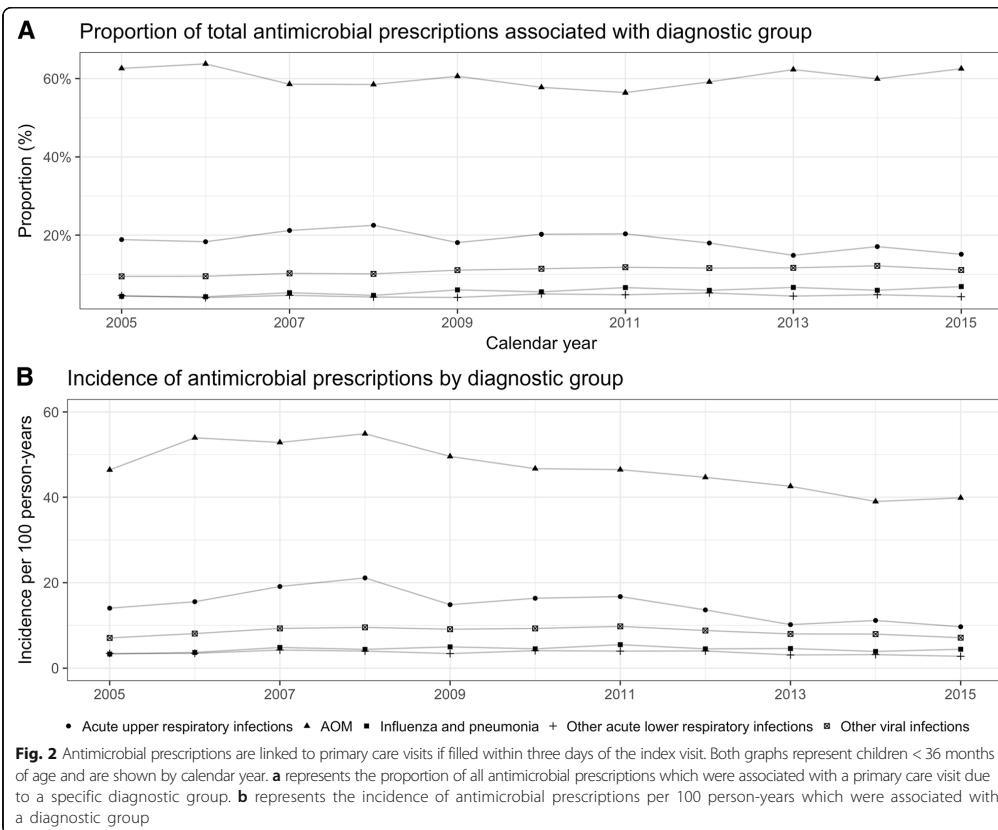
In the sub-analysis for AOM-associated antimicrobial prescriptions vaccine impact was calculated to be 21.8% (95%CI 11.5–30.9%). Additional file 3: Figure S2 shows HRs for each of the birth-cohorts compared to the 2010-reference cohort.

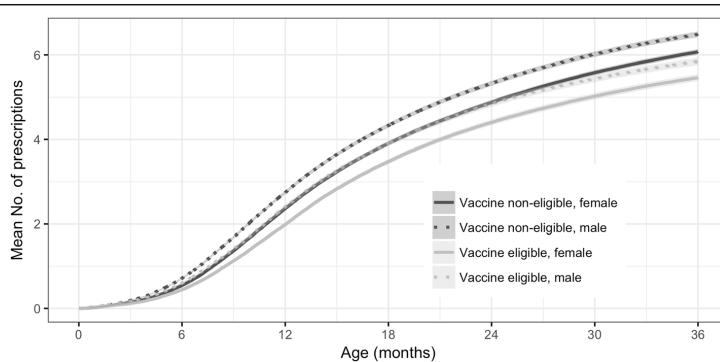
## Discussion

This population based study of 11 consecutive birth-cohorts followed until three years of age demonstrates a 5.8% reduction in all-cause outpatient antimicrobial prescriptions associated with the inclusion of PHiD-CV10 into the national paediatric vaccination program. We show that a relatively stable proportion of AOM visits result in antimicrobial prescriptions and that AOM is the most common indication for antimicrobial prescriptions in this age group. The impact of PHiD-CV10 on AOM-associated antimicrobial prescriptions was estimated 21.8%. Our group has previously demonstrated a 22% reduction in AOM visits following PHiD-CV10 introduction in Iceland [23]. Thus, a reduction in AOM episodes is a likely explanation for the reduction in all-cause antimicrobial prescriptions noted in this study. Age specific incidence rates of antimicrobial prescriptions were calculated for each birth-cohort and show a significant decrease in prescriptions in all age-groups following vaccine introduction. Also, the mean number

**Table 4** The proportion and 95% confidence interval for the vaccine non-eligible cohorts (VNEC, born: 2005–2010) and the vaccine eligible cohorts (VEC, born 2011–2013) that had filled 0, 1–4, 5–9, 10–14 and  $\geq 15$  prescriptions at 36 months of age. Only children with full 36 months follow-up were included

Number of prescriptions	Incidence proportion (%)		Incidence risk ratio (95%CI)
	VNEC	VEC	
0	11.4	13.2	1.16 (1.10–1.23)
1–4	43.7	47.3	1.08 (1.06–1.11)
5–9	31.6	29.1	0.92 (0.89–0.95)
10–14	9.8	7.5	0.77 (0.72–0.82)
$\geq 15$	3.5	2.9	0.83 (0.74–0.93)
Total	100	100	





**Fig. 4** Expected mean number of prescription per child for the vaccine non-eligible cohorts (VNEC, born 2005–2010) and the vaccine eligible cohorts (VEC, born 2011–2015), for both genders from birth to third birthday. Lines represent point estimates and shaded area the 95% confidence intervals

of outpatient antimicrobial prescriptions for both the VNEC and VEC was estimated as a function of age and a significant decrease in both genders was demonstrated.

RCT have shown significant vaccine efficacy of PCVs against outpatient antimicrobial consumption, with outcomes ranging from 5.4% (95%CI 4.0–6.7) [25] to 8% (95%CI 1–14) [26] and 15% (95%CI 3–25) [24]. Our results are within the lower bounds of these findings. Though blinded RCT provide robust estimates of vaccine efficacy, they do so under artificial conditions. Parents and physicians may behave differently knowing that their actions are being observed and quantified by researchers, and this may reduce the incidence of inappropriate prescribing. Observational studies are valuable in demonstrating that vaccine impact against outpatient antimicrobial prescriptions can still be observed in true clinical settings. Several observational studies have previously assessed the change in antimicrobial prescriptions following PCV introduction, demonstrating a 20–42% decrease in AOM-associated prescriptions in children < 2 years of age [8, 21] and a 5–24% decrease in all-cause antimicrobial prescriptions in older children [30, 31]. These findings are in agreement with our results.

The present study has several strengths, chiefly in the inclusion of the whole population of children under three years of age. Because all Icelandic children in 11 consecutive birth-cohorts are included, the possibility of sampling bias is eliminated. In Iceland, antimicrobials for systemic use are exclusively available by physician prescription. When a prescription is dispensed at any pharmacy in Iceland, information about the prescription is sent electronically to the NPD. The prescription is linked to the individual child's national identification number which allows observation of prescriptions by individual children regardless of location or time.

By using all-cause antimicrobial consumption as the outcome measure without attempting to exclude cases unlikely to be attributable to diseases caused by pneumococci, no positive bias is introduced through case ascertainment. The fact that antimicrobial consumption in Iceland is close to the average for European countries [32] further generalizes the results of the study.

The PHiD-CV10 was introduced in 2011 into the routine childhood vaccination program without a catch-up schedule. The uptake was immediately high with over 97% of each vaccine eligible birth-cohort receiving ≥2 doses [27]. Prior to the introduction of PHiD-CV10, no systematic vaccination against pneumococcus was in place. Between 0 and 1.9% of birth-cohorts 2005–2008 received ≥2 doses of PCV, and this proportion increased to 6.9% and 18.7% in birth-cohorts 2009 and 2010 [27]. The increase in vaccine uptake in birth-cohorts 2009 and 2010 is likely due to heightened awareness of the impending inclusion of PHiD-CV10 into the vaccination program, with many parents and caregivers opting to pay out-of-pocket for the vaccine. This clear differentiation in vaccine coverage between the vaccine non-eligible birth-cohorts and vaccine eligible birth-cohorts permits the use of the cohorts as a proxy for vaccination status.

Finally, as the data was identifiable to the individual, it allowed the use of more sophisticated survival analysis methods which are normally reserved for non-observational studies. This allowed for the complex interaction between age, gender and the number of previous antimicrobial prescriptions to be considered when estimating the vaccine impact. A crude incidence rate analysis was also performed (Fig. 1). Such an analysis necessitates the creation of discrete age-groups for comparison as the incidence of antimicrobial prescription varies by age and some of the VEC have censored follow-up time. The

results of the individual level analysis demonstrate that the vaccine decreased the risk of the first, second and third antimicrobial prescriptions. However, the vaccine was not associated with a further decrease in risk in those who had already filled  $\geq 4$  prescriptions. This provides evidence for a cumulative effect and is congruent with the results of the crude incidence analysis where the difference is most evident in the older age-groups. Because age is discretized in the crude analysis, the cumulative effect is not estimated and the vaccine impact is less apparent. Using the individual level analysis, it was also possible to demonstrate the mean number of prescriptions by age, taking gender, vaccine eligibility and number of previous prescriptions into account. Interestingly, antimicrobial consumption was significantly higher in boys than girls. The mean number of prescriptions for boys decreased significantly following vaccine introduction, becoming the same as that of girls prior to the vaccination (Fig. 4). This gender difference may be attributed to the fact that AOM is more common in boys than girls [33].

When children in the VEC were stratified by vaccination status, rather than birth-cohort, an abnormally high proportion of children who neither visited a physician nor filled an outpatient antimicrobial prescription was concentrated among those who did not have a documented vaccine dose. This is likely due to either under documentation of administered vaccine doses or children emigrating from Iceland without an official change in legal residence. Children who are for any reason unable to experience the study event, i.e. fill an outpatient antimicrobial prescription, are for the same reason likely to be unable to have a documented administered vaccine dose. This precluded an analysis using individual vaccination status to directly estimate the vaccine impact.

A significant downward trend in antimicrobial consumption was noted during the pre-vaccination era, with the final VNEC having significantly lower consumption than birth-cohorts 2005–2007 and non-significantly less consumption than birth-cohorts 2008 and 2009. Several contributing factors may contribute to these trends. Firstly, as mentioned above, the vaccine-uptake in the 2010 birth-cohort was noticeably higher than for the previous birth-cohorts. Theoretically, this could result in underestimation of the vaccine impact. However, the hazard ratio of antimicrobial prescription between the 2008 birth-cohort, of which only 1.8% had received  $> 2$  PCV doses, and the 2010 birth-cohort was non-significant (HR 1.02 95%CI 0.98–1.06) which suggests that the 18.7% vaccination coverage among children in the 2010 birth-cohort did not introduce significant negative bias to the vaccine impact estimate. Secondly, inappropriate prescribing may have decreased during the first half of the study period, after the Directorate of Health

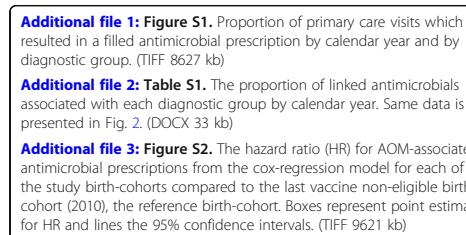
published new guidelines on diagnosis and treatment of AOM in 2009 [17]. However, as the majority of Icelandic doctors go overseas for specialist training (mostly Sweden, UK and USA), keeping up to date on respective guidelines and policy after returning back home to Iceland. This could result in gradual change in behaviour, starting prior to implementation, rather than sudden change. A study comparing outpatient antimicrobial use in European countries for 2004 and 2009 using drug-specific quality indicators found that the quality of antimicrobial prescriptions in Iceland was generally high. The quality increased between 2004 and 2009, rising in the European rankings from 12th to 7th place (out of 32) [34]. This may indicate that fewer inappropriate prescriptions were written, thus reducing prescriptions in general. However, we did not see evidence of increasing quality of prescriptions during the study period using the parameters available to us, e.g. proportion of episodes receiving prescriptions and the proportion of narrow-spectrum antimicrobials use. To ensure that no positive bias was introduced due to decreases occurring prior to vaccine initiation the vaccine impact was calculated using the last vaccine non-eligible cohort as the reference, even though 18.7% of those children had received  $> 2$  PCV doses.

As previously published by this study group, pneumococcal antimicrobial non-susceptibility is less common following the introduction of PhID-CV10 [35], and fewer children have required parenteral therapy for AOM [36]. Under these circumstances, one would have expected the use of narrow spectrum antimicrobials to increase. However, the opposite was found. In 2013 antimicrobials classified as second-line penicillins became the most prevalent antimicrobial class prescribed in Iceland. The most likely explanation for this is the removal of the amoxicillin suspension from the general market in Iceland between August 2013 and August 2015. Physicians could still prescribe the amoxicillin suspension, but it required a written form that was generally considered a nuisance as compared to the electronic prescription form to which Icelandic physicians had grown accustomed. Instead of an increased use of other suspensions within the first-line penicillin class, such as phenoxymethylpenicillin, the use of second-line penicillins (amoxicillin/clavulanic acid) and cephalosporins increased. As amoxicillin/clavulanic acid has a higher rate of adverse reactions compared to first line penicillins [37, 38] the removal of amoxicillin may have resulted in a substantial burden on children and their parents. In addition, at the end of the study period and 18 months after the reintroduction of amoxicillin into the general market, its use was still lower than before its removal. This warrants further investigation.

## Conclusions

The introduction of PHiD-CV10 lead to reduced antimicrobial use in children, which was mostly due to reduced episodes of acute otitis media. This intervention therefore not only reduces disease burden but could also slow the spread of antimicrobial resistance.

## Additional files



## Abbreviations

AOM: Acute otitis media; ATC: Anatomical therapeutic chemical; HR: Hazard ratio; ICD-10: International Classification of Diseases, 10th Revision; IR: Incidence rates; IRR: Incidence rate ratios; NPD: National Prescription Database; PCV: Pneumococcal conjugate vaccine; PHiD-CV10: 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine; RCT: Randomized controlled trials; URTI: Upper respiratory tract infections; VEC: Vaccine-eligible cohorts, VNEC: Vaccine non-eligible cohorts

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## Availability of data and materials

Not provided. The data is assembled from three large population based databases making data sharing problematic. In addition, the authors do not have permission to share these databases.

## Authors' contributions

Authors EE and SS contributed equally to this manuscript. EE conceptualized and designed the study, collected and analysed the data, performed the statistical analysis and interpretation. He drafted the manuscript and reviewed and revised it. SS conceptualized and designed the study, collected and analysed the data, participated in the statistical analysis and interpretation. He drafted the manuscript and reviewed and revised it. HE conceptualized and designed the study, obtained funding, reviewed and revised the manuscript. BH participated in the statistical analysis and reviewed the manuscript for statistical accuracy. AH and KGK conceptualized and designed the study and obtained funding. Participated in the writing of the manuscript, reviewed and revised it. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Ethics approval and consent to participate

The study was approved by The National Bioethics Committee (VSNb2013010015/03.07), the National Data Protection Authority (2013010100VEL—) and the Directorate of Health, Iceland (1,301,266/5.6.1/gkg). As this was a large epidemiological study where personal identifications were anonymised, obtaining informed consent was not required.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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## **Paper IV**



## REGULAR ARTICLE

## Increase in tympanostomy tube placements despite pneumococcal vaccination, a population-based study

Elias Eythorsson<sup>1</sup>, Samuel Sigurdsson<sup>1</sup>, Helga Erlendsdóttir<sup>1,2</sup>, Birgir Hrafnelsson<sup>3</sup>, Karl G. Kristinsson<sup>1,2</sup>, Ásgeir Haraldsson (asgeir@lsh.is)<sup>1,4</sup> <sup>1</sup>Faculty of Medicine, University of Iceland, Reykjavík, Iceland<sup>2</sup>Department of Clinical Microbiology, Landspítali University Hospital, Reykjavík, Iceland<sup>3</sup>Department of Mathematics, University of Iceland, Reykjavík, Iceland<sup>4</sup>Children's Hospital Iceland, Landspítali University Hospital, Reykjavík, Iceland**Keywords**Conjugate vaccines, Middle ear ventilation, Otitis media, PHiD-CV vaccine, *Streptococcus pneumoniae***Correspondence**

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**ABSTRACT****Aim:** The aim was to estimate the impact of the 10-valent pneumococcal vaccine (PHiD-CV) on tympanostomy tube placements (TTP) in children under five years of age in Iceland.**Methods:** This population-based observational cohort study followed 11 consecutive birth-cohorts 2005–2015 from birth until their fifth birthday. Population registries were merged using national identification numbers. The risk of TTP was compared between birth-cohorts adjusted for the number of previous otitis media diagnoses and antimicrobial prescriptions. A Cox regression model was applied and the hazard ratio (HR) of TTP was estimated between each birth-cohort and the last vaccine non-eligible birth-cohort. The vaccine impact of PHiD-CV10 on TTP was estimated as 1-HR × 100%.**Results:** In total, 51 247 children were followed for 210 724 person-years, of which 14 351 underwent 20 373 procedures. The estimated vaccine impact on TTP was –6% (95% CI –16% to 2.7%). Children in the vaccine-eligible cohorts had fewer previous otitis media diagnoses and had been prescribed fewer antimicrobials prior to the procedure than children in the vaccine non-eligible cohorts.**Conclusion:** Despite high uptake of PHiD-CV10, tympanostomy procedures increased in Iceland during the study period. Vaccine-eligible children had milder disease prior to the procedure. The reason underlying these findings are speculative.**INTRODUCTION**

Tympanostomy tube placements (TTP) are the most common paediatric surgical procedure in high-income countries (1,2). The most frequently cited indications for TTP are persistent serous otitis media and recurrent acute otitis media (3,4). Studies have consistently demonstrated the benefit of TTP in the treatment serous otitis media (3,4) while evidence for their use in the treatment of recurrent acute otitis media is inconsistent (3,5).

Prior to the general introduction of pneumococcal conjugate vaccines, the most common pathogens causing recurrent acute otitis media were *Haemophilus influenzae* and *Streptococcus pneumoniae* (6). Three randomized controlled trials of pneumococcal conjugate vaccines

(PCV) evaluated the vaccine efficacy against TTP and revealed a trend towards fewer TTP in vaccinated children compared to unvaccinated, with vaccine efficacy estimates of 20.1% (95% CI 1.5% to 35.2%) (7), 6% (95% CI –14% to 23%) (8) and 13% (95% CI –2% to 26%) (9), respectively.

In 2011, the 10-valent pneumococcal *Haemophilus influenzae* Protein D conjugate vaccine (PHiD-CV, Synflorix®) was introduced into the paediatric vaccination programme in Iceland, with a two + one schedule given at

**Abbreviations**

ARD, Absolute risk difference; HR, Hazard ratio; IQR, Interquartile range; OM, Otitis media; PCV, Pneumococcal conjugate vaccine; PHiD-CV, The 10-valent pneumococcal *Haemophilus influenzae* Protein D conjugate vaccine; RR, Risk ratio; TTP, Tympanostomy tube placements; VEC, Vaccine-eligible cohort; VNEC, Vaccine non-eligible cohort.

**Key notes**

- Tympanostomy tube placements are the most common paediatric surgical procedure and are commonly performed at private outpatient clinics.
- In this whole-population cohort study, the incidence of tympanostomy tube placements increased following the introduction of PHiD-CV10.
- Children in the vaccine-eligible cohorts had fewer documented physician visits for otitis media and had received fewer antimicrobial prescriptions prior to the tympanostomy procedure.

three, five and 12 months of age. All children born in 2011 and later were eligible. Vaccine uptake was immediately high with over 97% of each eligible birth-cohort receiving the primary vaccination by their first birthday (10). No systematic pneumococcal vaccination programme had previously been implemented.

The aim of this study is to estimate the vaccine impact of PHiD-CV against TTP in children under five years of age in Iceland and estimate the change in risk factors in children prior to undergoing the procedure.

## METHODS

### Data sources

This study was an individual level observational cohort study of all outpatient TTP in Iceland, from 1 January 2005 to 30 December 2016. Consecutive birth-cohorts, 2005–2015 were included and followed from birth until 60 months of age or end of the study period.

Data were collected from three population-based registries and from Landspítali University Hospital's patient registry. The four registries were merged with Statistic Iceland's population registry, using unique national identification numbers. The population register contains demographic information, including gender, date of birth, immigration, emigration and death for every permanent resident of Iceland. Children who immigrated to Iceland after birth were excluded from the analysis. The observation time of children who emigrated was censored on the date of emigration. This allowed for accurate person-year at risk calculations.

Data on TTP were extracted from the Icelandic Health Insurance reimbursement database, using the reimbursement codes for TTP. The data included the calendar year and month of the procedure, the specific subtype of procedure and the surgeon's identification number. Additionally, information on all TTPs performed at Landspítali University Hospital was systematically extracted from the patient registry using procedural codes.

Data on primary care visits were obtained from the Primary Care Database of the Icelandic Directorate of Health, which covers all Primary Health Care Centres in Iceland. These data were only available until 31 December 2015. The Primary Care Database contains information on all primary care visits in Iceland. A visit was defined to be due to otitis media (OM) if an International Classification of Diseases, 10th Revision (ICD-10) diagnostic code for non-suppurative otitis media (H65), suppurative otitis media (H66), mastoiditis (H70) or perforation of tympanic membrane (H72) was recorded by the physician. Repeat visits within 30 days of the initial visit were assumed to be due to the same episode and were excluded from the analysis. Data on urgent care visits to the paediatric emergency department of the Children's Hospital Iceland during the same period were extracted from Landspítali University Hospital's patient registry using the same methodology.

Data on all filled prescriptions with the anatomical therapeutic chemical classification code J01 (antibacterials for systemic use) and subgroups were extracted from the National Drug Prescription Database of the Directorate of Health, which contains information on all outpatient drug prescriptions in the country.

### Statistical methods

Statistical analysis was stratified by birth-cohorts and aggregate cohorts based on vaccine eligibility. Birth-cohorts 2005–2010 were classified as vaccine non-eligible cohorts (VNEC) and birth-cohorts 2011–2015 as vaccine-eligible cohorts (VEC). Statistical analysis was performed in R statistics version 3.3.3. using the survival package (11).

Crude incidence rates of TTP per 100 person-years were estimated for each birth-cohort by 6-month age groups, and crude incidence rate ratios between the VEC and VNEC were calculated assuming Poisson variance. The cumulative incidence of TTP procedures in each birth-cohort was assessed using the Kaplan–Meier estimator and confidence intervals calculated using the log delta method. The risk of TTP was compared between birth-cohorts with respect to two measures of risk; the number of previous diagnoses of otitis media and the number of previous antimicrobial prescriptions. In the subset of children who had undergone a TTP procedure and had full follow-up time (birth-cohorts 2011 and earlier), the distribution in the count of visits and prescriptions prior to the child's first TTP was compared between VNEC and VEC using an overall Chi-Squared Test of Independence. When assessing the previous visits, the observation age was four years of age due to restricted data. If a significant overall difference was detected, the risk ratio (RR) and absolute risk difference (ARD) within each level of the risk factor was estimated and tested using Chi-squared Tests of Independence. This was repeated for 36 month follow-up time.

A Cox regression model was applied to the individual level data to accurately account for the influence of age and censored follow-up time. The hazard ratio (HR) of TTP was estimated between each of the study's birth-cohorts and the last VNEC (2010), which was used as a reference. The vaccine impact of PHiD-CV against TTP was then estimated as  $1 - (\text{the hazard ratio between the last vaccine-eligible cohort and the reference cohort}) \times 100\%$ . Additional Cox regression models that incorporated the number of previous otitis media visits and antimicrobial prescriptions as time-dependent covariates were fitted to further correct the vaccine impact estimate for confounding. The Cox regression model using the number of previous otitis media visits was censored at 31 December 2015 due to restricted data. Each Cox model was stratified by gender and accounted for the correlation between repeated observations of the same child with sandwich variance estimates. The study was approved by The National Bioethics Committee (VSNb2013010015/03.07), the National Data Protection Authority (2013010100VEL/–) and the Directorate of Health, Iceland (1301266/5.6.1/gkg). There was no patient or public involvement in this study.

## RESULTS

### Demographics

Information was available for 53 218 children born in 2005–2015. Of those, 1892 children immigrated to Iceland after birth and were therefore excluded from the analysis. A further 55 children were excluded due to lack of accurate information on their date of birth, and 24 children were excluded because their follow-up time was less than one month. The remaining 51 247 children were followed for a total of 210 724 person-years. A total of 14 351 children underwent 20 373 TTP procedures during the study period, 57% of whom were male. Study demographics are summarised in Table 1. The median age of the children at the time of their first TTP was 17 months (IQR 13–24). Of the children who underwent the procedure, 10 248 (71%) had only one TTP procedure, 2902 (20%) had two, and 1201 (8%) had three or more. Most of the procedures (98%) were performed in private outpatient clinics. The number of otolaryngologists performing outpatient TTP increased from 15 in 2005 to 2023 in 2016 with each surgeon performing a median of 123 (IQR 56.5–196) procedures per year (Table S1).

### Crude incidence rates and cumulative incidence of TTP between VNEC and VEC

The overall crude incidence rate of TTP for children under five years of age was significantly higher in the VEC compared to the VNEC, 10.6 and 8.7 procedures per 100 person-years, respectively, (IRR 1.20, 95% CI 1.17 to 1.24). The crude incidence rate was highest among children 12–17 months of age, ranging from 19.2 to 28.5 procedures per 100 person-years. A significant increase in the crude incidence rate between VNEC and VEC was noted in children 12–17 and 18–23 months of age. No significant change in other age groups was observed (Fig. 1).

The cumulative incidence of each birth-cohort that underwent at least one TTP procedure by five years of age was highest in children born in 2010 and the lowest in children born in 2006, 32% and 29%, respectively (Table 2, Figure S1).

The mean (median) number of visits to a primary care physician or paediatric emergency department for otitis media prior to TTP was 2.05 (2) visits in the VNEC compared to 1.72 (1) visits in the VEC and the overall distribution was significantly different ( $p < 0.001$ ). The proportion of children who had never visited a primary care physician or the paediatric emergency department for otitis media prior to the TTP procedure, increased from 21% of children in the VNEC to 29% of children in VEC (RR 1.40, 95% CI 1.28 to 1.54). Conversely, children in the VNEC who underwent TTP were significantly more likely to have visited a physician because of otitis media twice and three times prior to the procedure compared to children in the VEC (Table 3, Table S2).

The mean (median) number of previous prescriptions was lower for VEC than VNEC, 3.19 (4) and 3.62 (4), respectively, and the distribution between the groups was significantly different ( $p < 0.001$ ). Children in the VEC were more likely to have never been prescribed antimicrobials, compared to VNEC, 5% vs 3% (RR 1.52, 95% CI 1.18 to 1.96).

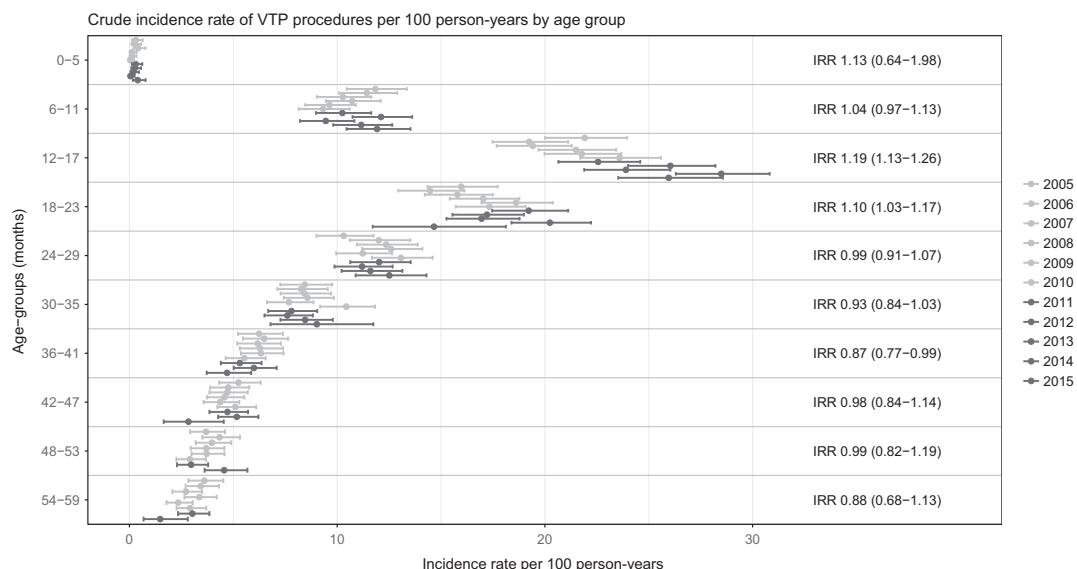
### Hazard ratio of TTP between VNEC and VEC

Model diagnostics of all Cox regression models did not reveal significant deviations from the model assumptions. Children who had visited a primary care physician for otitis media once had a HR of 3.12 (95% CI 2.93 to 3.32) for TTP compared to children who had never visited a physician. Children who had one previous antimicrobial prescription had a HR of 6.98 (95% CI 6.13 to 7.95) for TTP compared to those who had never received a prescription. The results of the three Cox models are illustrated in Figure 2. The hazard of TTP increased gradually from birth-cohort 2005 to 2015 irrespective of correction for previous otitis media visits or antimicrobial prescriptions. There was a slight pause in the rise in the hazard of TTP in the first vaccine-eligible cohorts in all Cox models. Using the pre-specified estimate, the estimated vaccine impact on TTP was –6% (95% CI –16% to 2.7%).

**Table 1** Demographic information about the study birth-cohorts

Birth-cohort	Number of children	Person-years	Number of procedures (number of children)	Median age in months (IQR)
2005	4541	21 409	1946 (1280)	17 (12–25)
2006	4665	21 988	1931 (1303)	18 (13–27)
2007	4770	22 500	1974 (1335)	18 (13–27)
2008	4949	23 313	2140 (1428)	18 (13–26)
2009	5128	24 141	2145 (1514)	18 (13–25)
2010	4984	23 580	2203 (1547)	18 (13–26)
2011	4641	22 052	1997 (1382)	18 (13–24)
2012	4667	20 191*	2057 (1419)*	16 (12–23)*
2013	4438	14 951*	1642 (1200)*	16 (13–23)*
2014	4438	10 731*	1582 (1251)*	16 (13–23)*
2015	4026	5866*	756 (692)*	13 (11–15)*
Total	51 247	210 723	20 373 (14 351)	17 (13–24)

The number of tympanostomy tube procedures is shown along with the total number of children who underwent at least one procedure. The median age at the time of the child's first procedure is provided. Birth-cohorts 2012–2015 did not reach full five-year follow-up time due to censoring. Values which are not directly comparable to previous birth-cohorts due to censoring are marked with an asterisk (\*).



**Figure 1** The incidence rate of tympanostomy tube procedures per 100 person-years for each birth-cohort is depicted, stratified by six-month age groups. Estimates are illustrated as points with error-bars indicating 95% confidence intervals. Vaccine non-eligible cohorts (VNEC) are illustrated in light grey and vaccine-eligible cohorts (VEC) in dark grey. The incidence rate ratios between VEC and VNEC are written along with 95% confidence intervals.

**Table 2** The cumulative incidence of each birth-cohort that has undergone at least one tympanostomy tube placement (TTP) by six-month age intervals

Birth-cohort	6 m (%)	12 m (%)	18 m (%)	24 m (%)	30 m (%)	36 m (%)	42 m (%)	48 m (%)	54 m (%)	60 m (%)
2005	0.4	7.2	16.4	21.1	23.7	25.8	26.9	27.8	28.4	28.8
2006	0.3	7.1	14.8	19.5	22.9	24.8	26.5	27.4	28.3	28.6
2007	0.4	6.6	14.9	19.7	23.4	25.3	26.7	27.8	28.4	28.6
2008	0.2	7.2	15.9	21.0	24.5	26.5	27.7	28.5	29.1	29.5
2009	0.3	6.5	15.7	22.0	25.1	27.2	28.5	29.1	29.9	30.2
2010	0.1	6.6	16.5	22.4	26.3	28.8	30.1	31.0	31.4	31.7
2011	0.4	6.6	16.3	23.3	26.3	27.9	28.7	29.4	30.1	30.5
2012	0.2	7.8	18.3	23.9	26.7	28.3	29.5	30.4	30.9	—
2013	0.3	6.5	16.3	21.7	25.0	26.9	27.5	—	—	—
2014	0.2	6.9	19.1	26.1	29.1	—	—	—	—	—
2015	0.5	7.8	18.6	—	—	—	—	—	—	—

Birth-cohorts 2005–2010 are vaccine non-eligible cohorts (VNEC), and birth-cohorts 2011–2015 are vaccine-eligible cohorts (VEC). Birth-cohorts 2012–2015 did not complete the full five-year follow-up time. In those cases where no child in the birth-cohort reached the beginning of the six-month age interval during the study period, the unknown proportion is represented with a hyphen (—).

## DISCUSSION

This observational cohort study of 11 consecutive birth-cohorts from 2005 to 2015 demonstrated an unusually high incidence rate of TTP among young Icelandic children. Both the incidence and cumulative incidence of TTP increased over the study period despite the introduction of PHID-CV. Children in the vaccine-eligible cohorts who underwent the procedure had visited a physician less often for the treatment of otitis media and had filled antimicrobial prescriptions than children in the VNEC, before undergoing the procedure. The largest increase in the incidence of

TTP was observed in children 12–17 and 18–23 months of age, despite a considerable reduction in the incidence of acute otitis media in those age groups (10).

These results are unexpected. Our research group has previously published studies on the impact of the PHID-CV vaccination programme in Iceland showing a 24% decrease in paediatric emergency department visits for otitis media (12), a 22% decrease in all-cause acute otitis media in primary care (10), a 6% decrease in all-cause outpatient antimicrobial prescriptions (13) and a 55% reduction in otitis media with treatment failure, as measured by the

**Table 3** The cumulative number of previous otitis media visits and antimicrobial prescriptions are shown for those children in the vaccine non-eligible cohorts (VNEC) and the vaccine-eligible cohorts (VEC) who underwent at least one tympanostomy tube placement

Cum No.	Previous visits for otitis media			Previous antimicrobial prescriptions		
	VNEC % (n)	VEC % (n)	RR (95% CI)	VNEC % (n)	VEC % (n)	RR (95% CI)
Zero	20.6 (1716)	28.9 (398)	1.40 (1.28 to 1.54)	3.4 (286)	5.2 (72)	1.52 (1.18 to 1.96)
One	24.9 (2076)	24.4 (337)	0.98 (0.89 to 1.09)	11.6 (966)	12.8 (177)	1.11 (0.95 to 1.29)
Two	20.4 (1705)	19.6 (270)	0.96 (0.85 to 1.07)	19.3 (1608)	22.6 (311)	1.27 (1.05 to 1.30)
Three to four	24.9 (2075)	20.2 (279)	0.81 (0.73 to 0.91)	37.8 (3154)	37.4 (516)	0.99 (0.92 to 1.07)
Five to seven	8.0 (666)	6.4 (89)	0.81 (0.65 to 1.00)	22.3 (1860)	19.3 (266)	0.87 (0.77 to 0.97)
Eight or more	1.2 (104)	0.4 (6)	0.35 (0.15 to 0.79)	5.6 (468)	2.7 (37)	0.48 (0.34 to 0.67)

The proportion of each cohort who had the corresponding number of prior visits or prescriptions is shown with the absolute number of children within parentheses. The relative risk (RR) of having each number of previous visits or prescriptions between the VEC and VNEC is shown with 95% confidence intervals.

incidence of ceftriaxone use for otitis media (14). Taken together, these results strongly indicate a reduction in the burden of disease associated with otitis media following PHiD-CV introduction. This however is not reflected in a decrease in TTP, as demonstrated by the current study.

Three randomized controlled trials have evaluated the effect of PCV on rates of TTP. In the Northern California Kaiser Permanente trial, 37 868 children were randomized in a double-blinded study to receive either PCV7 or meningococcus type C vaccine. A 20.1% (95% CI 1.5% to 35.2%) reduction in TTP was noted in the PCV7 cohort compared to the control (7). A similar trial conducted in Finland randomized 1662 children to receive either PCV7 or Hepatitis B vaccine and followed them with repeat examinations up to 24 months of age. A non-significant odds ratio 0.94 (95% CI 0.77 to 1.14) for TTP in the PCV7 was demonstrated (8). Finally, in Finland in 2014, a cluster randomized trial in which over 47 000 children were randomized to either PHiD-CV or Hepatitis B vaccine, found a non-significant decrease of 13% (95% CI -2% to 26%) (9). Observational studies have generally shown a decrease in TTP following vaccination. TTP was shown to have decreased by 16% (95% CI 11% to 21%) and 23% (95% CI 10% to 35%) in Tennessee and New York, respectively, following PCV7 introduction (15). Similarly, there was a 23%, 16% and 6% reduction in rates of TTP in children under one, one and two years of age in Australia following PCV7 introduction (16). However, not all countries have seen decreases following PCV introduction. Denmark implemented PCV7 in a two + one schedule into their paediatric vaccine scheme in October 2007. They have noted increasing TTP rates since 1998, and this upward trend remained unchanged following vaccine introduction (17).

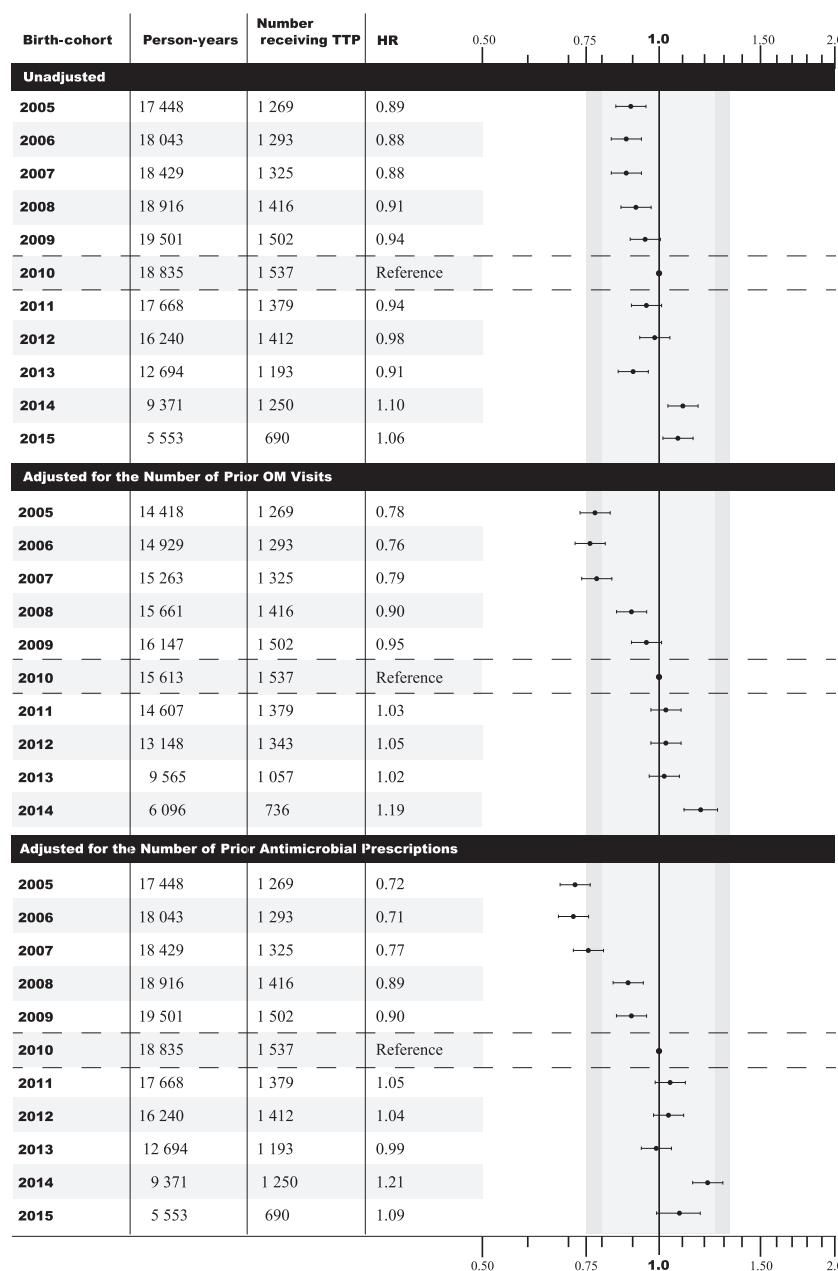
Our study confirms the previously reported high incidence rate and prevalence of TTP in Iceland, compared to other countries. The prevalence of children one to six years of age who underwent one or more TTP in Iceland was 29% in 1998 (18) and 34% in 2003 (19). Our data show that 31% of children in the latest birth-cohort with full five years of follow-up had undergone TTP. This is higher than; Australia (6% of five-year-old children) (20); Canada (7% of three-year-olds) (21); Denmark (29% of five-years-olds) (22);

Norway (9% of four-year-olds) (23); Sweden (1% of ten-year-olds) (24) and USA (7% of three-year-olds) (25).

These numbers are concerning. It is difficult to explain the reasons for a continued increase in the number of TTP performed in a country that already has one of the highest incidence of these procedures in the world (18,19). The burden of otitis media is dwindling, while the proportion of children undergoing the procedure is rising. The children in the VEC had fewer diagnoses of otitis media and were prescribed fewer doses of antimicrobials than children in the VNEC prior to the procedure, and thus seem to have less severe disease. All antimicrobial prescriptions regardless of provider or indication were included. However, patient data on visits to otolaryngologists and paediatricians in independent practice were unavailable due to coding differences and may be considered a confounder.

Data from Statistics Iceland's website show that visits to private practicing specialists have increased in Iceland, including visits to paediatricians and otolaryngologists. It is possible that a portion of non-emergent cases has moved from primary care to specialist care. Nevertheless, after-hours and urgent visits to private paediatricians were unchanged during the study period (personal correspondence with head of largest private paediatrician clinic), which suggests that paediatricians do not see acutely ill children with otitis media more often than previously. No urgent or after-hour clinic is operated by otolaryngologists.

Health care in Iceland is a single-payer system with the government guaranteeing equal access for all permanent residents through a single national health insurance scheme. Healthcare providers are either salaried governmental employees or independent practitioners who work within a framework agreement with Icelandic Health Insurance, and are reimbursed on a per case basis, according to pre-determined negotiations. There are no set regulations regarding the indication for, or the number of TTPs which may be performed annually at clinics in Iceland, and patients did not require a referral to make an appointment during the study period. The number of operating otolaryngologists increased during the study period. The out-of-pocket fee for TTP is low, a nominal outlay in a high-income country. Furthermore, data from Statistics Iceland's website show that the employment for



**Figure 2** The hazard ratio (HR) of tympanostomy tube placement between each birth-cohort and the last vaccine non-eligible birth-cohort are depicted, as estimated by three Cox regression models. At the top, unadjusted HR estimates are illustrated. HR estimates adjusted for the number of prior otitis media visits compromises the middle and prior antimicrobial prescriptions are illustrated at the bottom.

both genders has increased in recent years, and is among the highest in Europe (26). This may account for increased parental pressures for early intervention to avoid work absence. Antimicrobial usage, which like other paediatric interventions, may often be driven by parental pressure (27,28), is also comparably high in Iceland, but has decreased following the introduction of PHiD-CV (13).

There were two main limitations to our study. First, as discussed above, we were unable to include visits to specialists in this study. Second, as with any vaccine ecology study we cannot exclude the possibility of unmeasured confounding. Because the data are extracted from a reimbursement database, we do not have information concerning the indications for TTP. We therefore cannot exclude the possibility that, during the study period, there has been a shift towards indications that are not associated with the number of previous otitis media diagnoses in primary care or antimicrobial usage. However, we are unaware of any evidence supporting this hypothesis. Even if it were the case, there is evidence to suggest that PCV decreases both recurrent acute otitis media and serous otitis media (8,29). This study group has previously shown that recurrent acute otitis media has decreased in Iceland following the introduction of PHiD-CV10 (10). There is an increasing trend in the incidence of TTP in the vaccine non-eligible cohorts among children 12–17 and 18–23 months of age, as seen in Figure 1. However, interpreting changes in specific age groups within cohorts must be done with caution. Whether or not a child has a procedure at a young age modifies his or her risk of having a procedure later, and therefore a survival analysis approach was age is taken into account is more appropriate. The hazard of TTP is also shown to increase in the VNEC in Fig. 2. Visually, the increasing trend then seems to plateau in vaccine-eligible cohorts. It is possible that the incidence and cumulative incidence of TTP would have increased more sharply, had PHiD-CV10 not been introduced. The current study's design is however unable to provide evidence for or against this hypothesis.

The study has several strengths. The study population is well defined, including every child in the age group in the entire country. Individual level data on all TTP reimbursements spanning the six years before and after the vaccine introduction were extracted from databases of the Icelandic Health Insurance, which is the only Health Insurance provider in the country. This fact enables the accurate analysis of prevalence rate, incidence rates, incidence proportions and survival rate of TTP. In addition, it makes possible an accurate depiction of the burdens of the disease in children prior to receiving tubes, and of the indications for the procedures and the risk factors involved.

## CONCLUSION

The incidence, cumulative incidence and hazard of TTP increased significantly during the study period, which spans a six-year period before and after the introduction of the PHiD-CV into the Icelandic paediatric vaccination

programme. There was some evidence of increasing trend prior to vaccine introduction, which did not appear to have an impact on the incidence of TTP procedures. The reason for this is unclear and is neither in concordance with other studies evaluating PCV impact on TTP, nor does it reflect previous studies on the impact of PHiD-CV in Iceland. Our results suggest that children with softer indications or milder disease are receiving TTP. Further research is warranted. The data underlying the current study can be used to evaluate the impact of TTP on the risk of future otitis media and antimicrobial prescriptions compared to match children. The results could then be used to inform the development of national guidelines regarding the indication for tympanostomy tube placements.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose relevant to this article other than above.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article:

**Figure S1** The cumulative incidence of tympanostomy tube placements from birth to 60 months of age is shown for children in the vaccine non-eligible cohorts (illustrated in light grey) and the vaccine-eligible cohorts (illustrated in dark grey).

**Table S1** A summary of the study data by calendar year. The number of tympanostomy tube placements (TTP) performed on Icelandic children younger than five years of age is shown with the number of children undergoing at least one procedure presented within parentheses.

**Table S2** The absolute risk difference (ARD) in the number of previous otitis media visits and antimicrobial prescriptions between the vaccine non-eligible cohorts (VNEC) and the vaccine eligible cohorts (VEC).

**Table S3** The risk ratio (RR) and the absolute risk difference (ARD) in the number of previous otitis media visits and antimicrobial prescriptions between the vaccine non-eligible cohorts (VNEC) and the vaccine eligible cohorts (VEC).

**Paper V**



1   **Impact of the 10-valent pneumococcal conjugate vaccine on hospital**  
2   **admissions in children under three years of age in Iceland**

3

4   **Abstract**

5   **Introduction:** The pneumococcus is an important respiratory pathogen. The 10-  
6   valent pneumococcal vaccine (PHiD-CV) was introduced into the Icelandic  
7   vaccination programme in 2011. The aim was to estimate the impact of PHiD-CV  
8   on paediatric hospitalisations for respiratory tract infections and invasive  
9   disease.

10   **Methods:** The 2005-2015 birth-cohorts were followed until three years of age  
11   and hospitalisations were recorded for invasive pneumococcal disease (IPD),  
12   meningitis, sepsis, pneumonia and otitis media. Hospitalisations for upper- and  
13   lower respiratory tract infections (URTI, LRTI) were used as comparators. The  
14   2005-2010 birth-cohorts were defined as vaccine non-eligible cohorts (VNEC)  
15   and 2011-2015 birth-cohorts as vaccine eligible cohorts (VEC). Incidence rates  
16   (IR) were estimated for diagnoses, birth-cohorts and age groups, and incidence  
17   rate ratios (IRR) between VNEC and VEC were calculated assuming Poisson  
18   variance. Cox regression was used to estimate the hazard ratio (HR) of  
19   hospitalisation between VNEC and VEC.

20   **Results:** 51,264 children were followed for 142,315 person-years, accumulating  
21   1,703 hospitalisations for the respective study diagnoses. Hospitalisations for  
22   pneumonia decreased by 20% (HR 0.80, 95%CI:0.67-0.95) despite a 32%  
23   increase in admissions for LRTI (HR 1.32, 95%CI:1.14-1.53). Hospital  
24   admissions for culture-confirmed IPD decreased by 93% (HR:0.07, 95%CI:0.01-

25 0.50) and no hospitalisations for IPD with vaccine-type pneumococci were  
26 observed in the VEC. Hospitalisations for meningitis and sepsis did not change.  
27 A decrease in hospital admissions for otitis media was observed, but did not  
28 coincide with PHiD-CV introduction.

29 **Conclusion:** Following the introduction of PHiD-CV in Iceland, hospitalisations  
30 for pneumonia and culture confirmed IPD decreased, despite a marked increase  
31 in the incidence of other LRTI.

32  
33  
34 **Introduction**

35 Worldwide mortality in children under five years of age from acute lower  
36 respiratory tract infections (LRTI) is estimated to be 105 per 100,000 children,  
37 which translates to 700 thousand deaths annually. More than half are estimated  
38 to be due to pneumonia caused by *Streptococcus pneumoniae* [1]. Mortality  
39 rates vary greatly between countries, ranging from 0.65 per 100,000 children in  
40 Finland to 547 per 100,000 in Somalia, and have decreased by 37% globally  
41 since 2005 [1]. Hospitalisation rates for paediatric pneumonia also vary between  
42 countries. Immediately before a pneumococcal conjugate vaccine (PCV) was  
43 introduced into the national immunization programs, the rate of paediatric  
44 hospitalisations for pneumonia was 293 per 100,000 in Scotland[2], 615 per  
45 100,000 in Sweden[3] and up to 1274 per 100,000 in the US[4]. Pneumococci  
46 are the causative agent of 9-30% of community-acquired pneumonias in  
47 children, and this proportion is higher in severe cases [5–9]. Pneumococci are  
48 also among the most common bacterial causes of meningitis and sepsis in  
49 children, which are associated with high morbidity and mortality[10]. Other

50 clinical presentations of pneumococcal infections are more common and less  
51 severe. Otitis media (OM) is one of the most common reasons for both physician  
52 visits [11] and antimicrobial prescriptions[12] in young children. However, it is  
53 rare that OM and other acute upper respiratory tract infections (URTI) result in  
54 hospital admissions[13].

55 Pneumococcal conjugate vaccines have been widely incorporated into  
56 national immunization programs in recent years, and have been successful in  
57 reducing both invasive and non-invasive pneumococcal disease[2–4,11,13–18].  
58 The 10-valent pneumococcal *Haemophilus influenzae* protein-D conjugated  
59 vaccine (PHiD-CV) was introduced into the Icelandic national immunisation  
60 programme in 2011 for all children born 2011 and later, in a 2+1 schedule  
61 without a catch-up (at three, five and twelve months of age). Prior to the  
62 introduction of PHiD-CV, no systematic pneumococcal vaccination had been  
63 implemented. Vaccine uptake was excellent, with >97% of children in the  
64 vaccine eligible cohorts receiving the primary doses before their first  
65 birthday[19]. The aim of this study was to estimate the vaccine impact on  
66 admissions to the Children's Hospital in Iceland for culture-confirmed invasive  
67 pneumococcal disease (IPD), and all-cause meningitis, sepsis, pneumonia and  
68 OM.

69

70 **Methods**

71 **Data sources**

72 This study is a single-centre, individual-level, observational cohort study of  
73 paediatric hospital admissions due to IPD and diseases commonly caused by *S.*  
74 *pneumoniae*; all-cause OM, pneumonia, sepsis and meningitis. Hospitalisations  
75 for URTI and other LRTI as well as all-cause hospital admissions, were used as  
76 comparators. The Children's Hospital Iceland is the primary paediatric hospital  
77 for approximately 90% of the Icelandic population ([www.statice.is](http://www.statice.is)) and serves as  
78 a secondary and tertiary paediatric hospital for the entire country.

79 Eleven consecutive Icelandic birth-cohorts 2005-2015 were followed from birth  
80 to three years of age, or until the end of the study period. Individual-level  
81 immigration and emigration data were collected from Statistics Iceland. Children  
82 who were born outside of Iceland and subsequently immigrated were excluded  
83 from the analysis. All hospital admissions to the Children's Hospital from 1  
84 January 2005 to 31 December 2016 were included.

85 Data on admissions were collected from the hospital inpatient registry. Seven  
86 diagnostic groups were defined, of which six were based on International  
87 Classification of Diseases, 10<sup>th</sup> Revision (ICD-10) discharge diagnoses (Table  
88 1). An admission was considered to be due to IPD if the admitted child had  
89 culture- or PCR-confirmed *S. pneumoniae* sampled from blood, cerebrospinal or  
90 joint fluids and bones, regardless of ICD-10 discharge diagnosis. These  
91 microbiological data were extracted from laboratory information system of the  
92 Department of Clinical Microbiology at Landspítali University Hospital, the  
93 national reference laboratory for Iceland.

95 Using national identification numbers, culture data were linked to admissions  
96 data on the individual-level. Data included the date of birth, age, sex, the dates  
97 of admission and discharge, intensive care unit (ICU) stay and discharge  
98 diagnosis. All positive cultures linked to hospital admissions were included.  
99 Additionally, aggregate data on all admissions to the Children's Hospital Iceland  
100 regardless of diagnosis were also collected, and the number of admissions and  
101 proportion admitted to ICU were recorded and compared to the study data.  
102 Demographic information was collected from Statistics Iceland ([www.statice.is](http://www.statice.is))

103 **Statistical methods**

104 All Icelandic children born 2005-2015 were followed from birth until three years  
105 of age, or until death, emigration or the end of the study period. Based on the  
106 eligibility criteria of the PHiD-CV programme, birth-cohorts 2005-2010 were  
107 grouped as vaccine non-eligible cohorts (VNEC) and birth-cohorts 2011-2015 as  
108 vaccine eligible cohorts (VEC). When appropriate, the mean age at the time of  
109 admission was calculated and compared between diagnostic groups using  
110 Welch's two sample t-test. A difference between birth-cohorts in the mean age at  
111 admission was tested using analysis of variance, followed by Tukey's honest  
112 significance test. The median length of stay was calculated and compared  
113 between diagnostic groups using the Wilcoxon rank sum test. The crude  
114 incidence rates (IR) of hospital admissions were calculated for each birth-cohort,  
115 diagnostic group and age group, and crude incidence rate ratios (IRR) were  
116 calculated between the VNEC and VEC assuming Poisson variance. The  
117 proportion of admissions leading to an ICU stay was calculated by birth-cohort  
118 and diagnostic group.

119 The Kaplan-Meier product limit estimator was used to calculate event-free  
120 survival between the VNEC and VEC. This portion of the analysis included only  
121 the first hospitalisation of each child for each diagnostic group. Subsequent  
122 hospitalisations were excluded. Follow-up time was censored on both emigration  
123 and death. Cox regression was used to estimate the hazard ratio (HR) of  
124 hospitalisation between the VNEC and VEC for each diagnostic group. To  
125 elucidate whether the observed differences were likely to be due to the direct  
126 effects of the PHiD-CV, the Cox regression was repeated in two restricted age-  
127 ranges; 0-90 days of age and 90 days and older. The sensitivity of the hazard  
128 ratio to potential unmeasured confounding was examined by calculating E-  
129 values[20]. An E-value represents the minimum association that an unmeasured  
130 confounder would need to have with both the exposure and the outcome, to be  
131 able to explain away the observed association completely.

132 The study was approved by The National Bioethics Committee  
133 (VSNb2013010015/03.07), The National Data Protection Authority  
134 (2013010100VEL--) and medical director at the University Hospital.

135 **Results**

136  
137 Information was available for 53,228 children born 2005-2015. Of those, 1,892  
138 were excluded because they had immigrated to Iceland after birth. A further 72  
139 were excluded because of missing information on birth-date. The remaining  
140 51,264 children were followed for a median of 1,096 days (range 6-1,096),  
141 resulting in 142,315 person-years of follow-up time. A total of 10,520 children  
142 had the follow-up time censored before their third birthday. Of those, 8,234 were

143 censored at the end of the study period, 2,263 were censored due to emigration  
144 and 23 because of death. Birth-cohorts ranged from 4,026 to 5,130 children, and  
145 51.3% were male.

146 A total of 1,414 children were admitted 1,703 times to hospital for  
147 diseases in the study's diagnostic groups, ranging from 98-160 children and  
148 105-219 hospitalisations per birth-cohort. The total number of admissions,  
149 regardless of diagnosis, is shown in Table 2.

150 **Admissions due to pneumonia and LRTI**

151 During the study period, 550 children were admitted 660 times with discharge  
152 diagnoses consistent with pneumonia. Hospital admissions due to LRTI were  
153 recorded 550 times for 508 children. The crude IR of admissions for pneumonia  
154 among children under three years of age was 4.94 and 4.18 per 1,000 person-  
155 years in the VNEC and VEC respectively. The analogous crude IR of admissions  
156 for LRTI was 2.94 and 5.23 in the VNEC and VEC.

157 The crude IR of pneumonia admissions was highest in children 12-17 months of  
158 age, with a significant decrease noted between the VNEC and VEC (crude IRR:  
159 0.52 (95%CI: 0.35-0.77, Figure 1). The IR of admissions for LRTI was highest in  
160 children <6 months of age, with a significant increase between the VNEC and  
161 VEC (crude IRR 1.50, 95%CI 1.23-1.84, Figure 1). The IR was unchanged in  
162 other age groups for both diagnoses (Figure 1).

163 Children admitted for other LRTI were significantly younger than children  
164 admitted for pneumonia (mean ages 8.0 and 13.6 months respectively,  $P<.001$ ).  
165 The mean age at admission for pneumonia was significantly lower for birth-

166 cohort 2012 (10.7 months) than for birth-cohort 2006 (17.7 months); the mean  
167 difference being 7 months (95%CI 0.9-13.1,  $P=0.01$ ). No differences were  
168 observed in the mean age at admission for pneumonia between other pairs of  
169 birth-cohorts, and no differences were observed in the age at admission for  
170 LRTI. The proportion of admitted children who were male was 52% and 53% for  
171 pneumonia and LRTI respectively. The length of hospital stay was significantly  
172 longer for pneumonia than for LRTI (median of 2.84 days IQR 1.7-4.9 compared  
173 to 2.58 days IQR 1.7-4.0,  $P<.001$ ). Children hospitalised for pneumonia were  
174 more likely to be admitted to the ICU (5% compared to 1%), though there was  
175 no significant difference in the length of ICU stay (median 1.31 days IQR 0.72-  
176 4.12 compared to 1.16 days IQR 0.65-1.56).

177 Within the pneumonia diagnostic group, the greatest reduction was noted for  
178 admissions associated with the ICD-10 discharge diagnosis J18 (pneumonia,  
179 organism unspecified). The rates of admissions for other ICD-10 discharge  
180 diagnoses within the pneumonia diagnostic group remained unchanged between  
181 the cohorts (Table 3).

182 For both LRTI and pneumonia hospitalisations, a clear difference in the  
183 cumulative admission rates per 1000 person-years was observed between  
184 VNEC and VEC (Figure 2). The hazard ratio of pneumonia hospitalisation  
185 between the VEC and VNEC was 0.80 (95%CI:0.67-0.95), with an E-value of  
186 1.81. When restricted to children younger than 90 days of age, and 90 days of  
187 age and older, the hazard ratio was 1.22 (95%CI 0.81-1.85) and 0.73 (95%CI  
188 0.60-0.89) respectively.

189 The hazard ratio for LRTI hospitalisations between VEC and VNEC was 1.32  
190 (95%CI:1.14-1.53) (Figure 3), with an E-value of 1.97 . The hazard ratio was  
191 larger when evaluated in children younger than 90 days of age, HR 1.54 (95%CI  
192 1.23-1.94), and was no longer significant in children 90 days and older, HR 1.18  
193 (95%CI 0.97-1.44).

194 **Admissions due to URTI and OM**

195 In total, 131 URTI hospitalisations of 123 children, and 280 OM hospitalisations  
196 of 256 children were observed. No significant change was noted between birth-  
197 cohorts in mean age at hospital admission for any of the diagnostic groups. The  
198 crude IR of admission for OM among children under three years of age was 2.32  
199 and 1.45 per 1,000 person-years in the VNEC and VEC respectively, and the  
200 crude IR for URTI admissions was 0.78 and 1.13 in the VNEC and VEC.

201 The mean age of children admitted for URTI was 13.5 months compared to 12.8  
202 months for OM (difference 0.79 months, 95%CI -1.41-2.98, P=.48). Of the  
203 children admitted for URTI and OM, 55% and 57% respectively were male. The  
204 median length of hospital stay was 1.9 days (IQR 1.5-3.7) for URTI admissions,  
205 and 2.0 (IQR 1.0-3.7) for OM admissions. Three children admitted for OM were  
206 transferred to the ICU; one with secondary mastoiditis and the other two for  
207 unrelated systemic illnesses. Five children admitted for URTI were transferred to  
208 the ICU with diagnoses of laryngitis or laryngotracheitis. The cumulative  
209 admission rate per 1000 person-years for URTI and OM are shown in Figure 2.

210 The hazard ratio of OM admission between the VEC and VNEC was 0.57  
211 (95%CI:0.43-0.73) with an E-value of 2.9. When restricted to children younger  
212 than 90 days of age, the hazard ratio was 0.72 (95%CI 0.33-1.57), and 0.55

213 (95%CI 0.42-0.72) among children 90 days and older. The hazard ratio for URTI  
214 hospitalisation was 1.56 (95%CI:1.11-2.19) (Figure 3), with an E-value of 2.49.  
215 Among children younger than 90 days, and 90 days and older, the hazard ratio  
216 was 3.4 (95%CI 1.72-6.90) and 1.13 (95%CI 0.75-1.71) respectively.

217

218 **Admissions due to all-cause meningitis, sepsis and IPD**

219 A total of 15 children were admitted to hospital 19 times for meningitis, and 61  
220 children 63 times for sepsis. The crude IR of meningitis hospitalisation was 16.5  
221 and 8.7 per 100,000 person-years in the VNEC and VEC respectively, and the  
222 crude IR for sepsis hospitalisations was 38.8 and 52.3. 23 hospitalised children  
223 had culture-confirmed IPD. The crude IR of IPD was 24.7 per 100,000 person-  
224 years in the VNEC compared to 1.74 per 100,000 person-years in the VEC. No  
225 vaccine-type IPD was identified in the VEC.

226 The mean age of children admitted for meningitis, sepsis and IPD was 9.7  
227 months, 8.4 months and 14.4 months respectively. The proportion of admitted  
228 children who were males was 67% for meningitis, 57% for sepsis and 65% for  
229 IPD. The median length of hospital stays for children admitted for meningitis was  
230 9.3 days (IQR 5.4-10.7), 6.1 days (IQR 3.8-9.3) for sepsis and 5.8 days (IQR  
231 4.1-6.8) for IPD. The proportion of admitted children requiring an ICU care was  
232 55% for meningitis, 6% for sepsis and 33% for IPD.

233 The cumulative admission rates per 1,000 person-years for sepsis and IPD are  
234 shown in Figure 2. For meningitis, the hazard ratio of hospitalisation between the  
235 VEC and VNEC was 0.45 (95%CI 0.15-1.41). An E-value was not computed as

236 the hazard ratio was not significant. The hazard ratio of hospital admission for  
237 IPD between VEC and VNEC was 0.07 (95%CI:0.01-0.50) with an E-value of  
238 28.06. The hazard ratio of sepsis hospitalisation between the VEC and VNEC  
239 was 1.26 (95%CI:0.75-2.13) (Figure 3). No E-value was calculated as the ratio  
240 was not significant. Restricted analyses in these three diagnostic groups did not  
241 alter results (data not shown).

242 **Discussion**

243 This population-based study of eleven consecutive Icelandic birth-cohorts  
244 demonstrated a 20% reduction in pneumonia hospitalisations among children  
245 younger than three years of age, following the nationwide introduction of PHiD-  
246 CV into the national immunisation program. Hospitalisations due to culture-  
247 confirmed IPD decreased by 93% and there were no hospital admissions due to  
248 vaccine-type IPD among the vaccine eligible cohorts. The vaccine impact on  
249 hospital admissions due to all-cause meningitis, sepsis and OM was ambiguous.

250 In this study, the vaccine impact of PHiD-CV for all-cause pneumonia  
251 hospitalisations was 20%. This is in line with previous studies examining the  
252 impact of PHiD-CV, which have demonstrated a 7.4-30% reduction for clinically  
253 diagnosed pneumonia [2,15,21,22]. The result is also reasonable when  
254 compared to a rough calculation of potential impact using literature estimates.  
255 Pneumococci have been estimated to be the causative agent in 30% of  
256 paediatric pneumonias in non-vaccinated populations [7,9,23]. Prior to the  
257 introduction of PHiD-CV in Iceland, 70% of pneumococcal isolates collected  
258 from the middle ear, lower respiratory tract and normally sterile sites in children  
259 younger than six years of age were of vaccine-type[24]. Previously, we have

260 reported a 96% reduction in carriage of vaccine-type pneumococci among  
261 children attending day-care centres following the PHiD-CV introduction in  
262 Iceland[25]. Using impact on carriage as a rough proxy for disease  
263 impact[26,27], and assuming that 30% of paediatric pneumonias are caused by  
264 pneumococci[7,9,23], of which 70% are assumed to be vaccine-type[24], the  
265 estimated vaccine impact on all-cause pneumonia would be 20.1%. This figure  
266 supports the validity of the our results.

267 As in any vaccine ecological study, careful consideration must be paid to the  
268 possibility of unmeasured variables unrelated to the vaccination which could  
269 influence the outcome. Because the study followed all children in Iceland for  
270 eleven consecutive birth-cohorts, there was no sampling bias. This means that  
271 differences in the distribution of risk factors among children in the VNEC  
272 compared to VEC could only be due to systematic changes in the whole  
273 population. We are unaware of any systematic changes that could have reduced  
274 the incidence of paediatric pneumonia requiring hospitalisation, except the  
275 introduction of PHiD-CV. Secular changes in the disposition of pneumonia cases  
276 could hypothetically explain the observed association, if physicians who  
277 previously tended to admit low-risk paediatric pneumonia, later tended to treat  
278 them as outpatients. If this was true, hospitalisations for other related diseases  
279 would be expected to concurrently decrease, due to the same cultural changes.  
280 The proportion of pneumonia hospitalisations admitted to the ICU and the  
281 hospital length of stay would be expected to increase, as the proportion of  
282 serious pneumonia cases would be higher. None of these predictions were  
283 observed (Table 2, Supplementary Table 1).

284 The E-value for the hazard ratio of pneumonia hospitalisations between the VEC  
285 and VEC was 1.81. An E-value represents the minimum amount by which a  
286 potential unmeasured confounder would need to be associated with the  
287 exposure (vaccine eligibility) and the outcome (paediatric pneumonia  
288 hospitalizations), to explain away the observed hazard ratio. We are not aware  
289 of any such systematic confounders. The slight decrease in the incidence rate of  
290 pneumonia hospitalisations in vaccine non-eligible birth-cohorts 2009 and 2010  
291 aged 12-17 months (Figure 1) is likely due to selective vaccination of high-risk  
292 children, which was implemented in the years prior to vaccine introduction. This  
293 is supported by our data, which show that 6% of children in the 2009 birth-cohort  
294 and 22% of the 2010 birth-cohort received two or more doses of a  
295 pneumococcal conjugate vaccine before their second birthday. Another plausible  
296 explanation for this decrease is that the 2010 birth-cohort reaped the benefits of  
297 coexisting with the younger, fully-vaccinated 2011 birth-cohort.

298 It is interesting that during the same period, a 32% increase in hospital  
299 admissions due to LRTI was noted. While differentiating between clinical  
300 pneumonia and other LRTI in young children can be challenging, we argue that  
301 the observed decrease in pneumonia is a true decrease, and not the result of a  
302 drift in diagnostic coding practices from pneumonia to other LRTI diagnoses.  
303 This conclusion is supported by the following arguments. Firstly, the study  
304 included only children admitted to the paediatric ward, thereby representing a  
305 subgroup of children with severe illnesses. The majority of these children  
306 underwent rigorous inpatient testing to confirm the diagnosis, including non-  
307 invasive culturing, blood cultures, blood tests and chest x-rays. This reduced the

308 risk of misdiagnosis. Secondly, while the increase in admissions due to LRTI  
309 was observed mainly in children younger than six months of age, the decrease  
310 in pneumonia admissions was mainly noted in children between 12 and 18  
311 months of age. This age group distinction suggests that the changes in the two  
312 diagnostic groups are independent, and not the result of a shift in diagnostic  
313 coding. Some studies suggest that receiving a dose of pneumococcal conjugate  
314 vaccine increases a child's immediate risk of viral pneumonia[28]. However,  
315 upon further examination, an increased risk of LRTI as a result of PHiD-CV  
316 introduction is unlikely. The analysis was restricted to children younger than 90  
317 days (before the first dose of PHiD-CV) and older than 90 days. In children  
318 younger than 90 days the hazard ratio of LRTI between VEC and VNEC was  
319 attenuated compared to the main-analysis. When restricting to older age than 90  
320 days, the HR between VEC and VNEC became insignificant. The increased  
321 hazard of LRTI in children in the VEC compared to the VNEC is therefore most  
322 apparent before children in the VEC receive a single dose of the vaccination.  
323 This observation strongly suggests that there is an explanation independent of  
324 the vaccination. Furthermore, the E-value for the hazard ratio was 2.49, which  
325 means that an unmeasured confounder would have to be associated with  
326 vaccine eligibility and risk of LRTI hospitalization by a factor of 2.49 to explain  
327 away the observed association. Unlike for paediatric pneumonia, the data  
328 suggest the presence of such an unmeasured confounder.

329 An increase in positive virology testing for RSV and human metapneumovirus  
330 was noted in Iceland in the post-vaccination era[29].Similarly, an increase in the  
331 incidence of LRTIs has been reported worldwide in recent years, possibly due in

332 part to a novel strain of respiratory syncytial virus (RSV) A of genotype ON1  
333 which surfaced in 2010 [30–33]. An increase in viral respiratory infections, such  
334 as those caused by RSV, influenza and human metapneumovirus generally  
335 result in an increase in pneumococcal acquisition[34,35]. This may lead to  
336 subsequent bacterial diseases, including OM, pneumonia and IPD[35–38].  
337 Because the incidence of LRTI was considerably higher in the VEC compared to  
338 the VNEC, the observed 20% decrease in the hazard of hospitalisation for  
339 pneumonia is more significant. This can be seen in both the crude incidence rate  
340 analysis and the Cox regression analysis.

341 The 93% reduction observed in admissions due to IPD reported was greater  
342 than the 55-83% reduction in IPD reported in other studies[15,39–44]. The  
343 decrease in IPD was evident right from the beginning of the study period, before  
344 the vaccination program was introduced (Figure 1). A secular trend in the  
345 incidence of meningitis in Iceland from 1975 to 2014 has previously been  
346 reported [45]. Likewise, a similar unknown process may have contributed to the  
347 decreasing incidence of IPD. Some of the observed decrease could be  
348 explained by vaccination of at-risk children, as has been previously discussed.  
349 Regardless, the E-value for the hazard ratio of IPD was 28.06. It is unlikely that  
350 an unmeasured confounder could be 28.06 times more associated with vaccine  
351 eligibility than not, and increase the risk of hospitalisation for IPD 28.06 times.

352 The present study was not able to detect an impact on all-cause meningitis and  
353 sepsis hospitalisations. This may be because of a too small sample size to  
354 detect a change, given the anticipated lesser effect of PHiD-CV on all-cause  
355 invasive disease.

356 The vaccine impact on OM hospitalisations was ambiguous. The estimated  
357 hazard ratio between VEC and VNEC was 0.57 (95%CI:0.43-0.73). However,  
358 this difference appeared to be driven by a sharp decrease in the incidence of  
359 OM hospitalisations among the first two birth-cohorts, well before even selective  
360 vaccination was common. The hazard ratio of OM admissions was significantly  
361 higher among birth-cohorts 2005-2007 compared to the last VNEC, the 2010  
362 birth-cohort. This seems to indicate that the rate of OM hospitalisations did not  
363 decrease following vaccine introduction.

364 Three observational studies demonstrated a decrease in OM hospitalisations  
365 following the introduction of a PCV [13,17,46]. In the USA, a large study  
366 compared the incidence of OM hospitalisations prior to the introduction of PCV7  
367 to the period following the introduction of PCV-13, and demonstrated a 66%  
368 relative risk reduction in children less than one year of age [13]. A Swedish study  
369 comparing admission rates prior to the introduction of PCV-7 to admission rates  
370 following the introduction of PHiD-CV/PCV13 reported a 42% reduction in  
371 hospital admissions for OM in children less than four years of age [17]. The  
372 largest decrease was seen in the first year following the introduction of PCV7,  
373 despite no catch-up schedule being implemented[3]. In Italy, 36.4% reduction in  
374 OM hospitalisation was noted in birth-cohorts eligible for the vaccination  
375 following PCV-7 introduction, compared to prior birth-cohorts [46]. None of the  
376 above studies considered the impact of decreasing trends in OM hospitalisations  
377 prior to the introduction of PCV or the possibility of unmeasured confounding. In  
378 our study, the importance of carefully interpreting the results with regard to  
379 secular trends and possible confounders was demonstrated to have significant

380 impact on the results. A recent Israeli study did not find a decrease in hospital  
381 admissions due to OM.[47]. Clinical practices in treating OM can vary greatly  
382 between countries and often depend on factors such as the feasibility of strict  
383 follow-up. In Iceland, outpatient treatment of OM is favoured over admissions  
384 whenever possible. Indeed, children discharged from hospital are frequently  
385 scheduled for reassessment the very next day. While further studies are  
386 required to determine the full extent of the impact of PCVs against OM  
387 admissions, the effect on OM in outpatient care has been well  
388 established[11,14,48,49].

389 Admissions due to URTI increased slightly in the VEC compared to the VNEC.  
390 Our data suggest that the increased risk was driven primarily by an increase in  
391 the youngest age group, that is, children too young to have received a single  
392 dose of PHiD-CV.

### 393 **Conclusion**

394 Our study demonstrates a significant impact of PHiD-CV on the rate of hospital  
395 admissions due to pneumonia and IPD among Icelandic children younger than  
396 three years of age, adding to the growing literature of the impact of PHiD-CV on  
397 pneumococcal diseases.

### 398 **Declarations:**

#### 399 **Ethics approval:**

400 The study was approved by The National Bioethics Committee  
401 (VSNb2013010015/03.07), the National Data Protection Authority  
402 (2013010100VEL--) and the Directorate of Health, Iceland (1301266/5.6.1/gkg)

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414   ÁH had full access to all of the data in the study and takes responsibility for the

415   integrity of the data and the accuracy of the data analysis.

416   Study concept and design: SS, ESE, HE, ÁH, KGK

417   Acquisition, analysis, or interpretation of data: SS, ESE

418   Drafting of the manuscript: SS, ESE

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- 627
- 628

Diagnostic group	Abbreviation	Definition
Meningitis	-	ICD-10 discharge diagnosis of G00
Sepsis	-	ICD-10 discharge diagnosis of A41 or A42
Pneumonia	-	ICD-10 discharge diagnosis of J09-J18
Otitis Media and Complications	OM	ICD-10 discharge diagnosis of H65, H66, H70 or H72
Acute Upper Respiratory Tract Infections	URTI	ICD-10 discharge diagnosis of J00-J06
Acute Lower Respiratory Tract Infections	LRTI	ICD-10 discharge diagnosis of J20-J22
Invasive pneumococcal disease	IPD	Microbiologically confirmed pneumococcal infection from normally sterile site, regardless of ICD-10 diagnosis

629      Table 1 Definition and summary of the study's diagnostic groups. When  
 630      applicable, the abbreviation used in the text is provided. Six of the seven  
 631      diagnostic groups were defined based on the International Classification of  
 632      Diseases, 10<sup>th</sup> Revision (ICD-10) codes associated with the hospitalisation.  
 633      Invasive pneumococcal disease (IPD) was defined as any hospitalisation  
 634      associated with positive pneumococcal culture from blood, cerebrospinal or joint  
 635      fluid.

636

Birth-cohort	Children followed, n	Follow-up time, person-years	All cause admissions, n	Study admissions, n (children, n)	Proportion due to study diagnosis, %	ICU admissions, n (children, n)
2005	4,541	13,278	446	219 (160)	49.1	7 (7)
2006	4,668	13,658	415	176 (140)	42.4	10 (8)
2007	4,770	13,985	423	186 (160)	43.9	6 (5)
2008	4,953	14,472	442	117 (101)	26.5	5 (4)
2009	5,130	14,965	484	124 (109)	25.6	7 (6)
2010	4,988	14,593	384	158 (138)	41.1	7 (7)
2011	4,643	13,638	392	129 (112)	32.9	4 (4)
2012	4,667	13,750	576	196 (155)	34.0	0 (0)
2013	4,438	13,033	472	149 (119)	31.6	9 (8)
2014*	4,440	10,916*	431*	144 (122)*	33.4	6 (5)*
2015*	4,026	6,027*	377*	105 (98)*	27.9	3 (3)*
Total	51,264	142.31	4,842	1,703 (1,414)		64 (57)

637 Table 2. Overview of admissions in the study birth-cohorts. Asterisk signifies  
 638 incomplete follow-up due to censoring at the end of the study period before all  
 639 children in the birth-cohort had reached 3 years of age.

640

	Vaccine non-eligible cohorts		Vaccine eligible cohorts		Comparison between VEC and VNEC
Sub-group diagnosis	n	IR (95%CI)	n	IR (95%CI)	IRR (95%CI)
J10: Influenza with pneumonia, virus identified	5	0.06 (0.02-0.14)	1	0.02 (0.00-0.10)	0.30 (0.01-2.65)
J11: Influenza with pneumonia, virus not identified	1	0.01 (0.00-0.07)	0	0.00 (0.00-0.06)	0.00 (0.00-57.76)
J12: Viral pneumonia	68	0.80 (0.62-1.01)	48	0.84 (0.62-1.11)	1.05 (0.71-1.53)
J13: Pneumonia due to <i>S. pneumoniae</i>	3	0.04 (0.01-0.10)	3	0.05 (0.01-0.15)	1.48 (0.20-11.06)
J15: Bacterial pneumonia, not elsewhere classified	90	1.06 (0.85-1.30)	55	0.96 (0.72-1.25)	0.91 (0.64-1.28)
J16: Pneumonia due to other infectious organisms	3	0.04 (0.01-0.10)	2	0.03 (0.00-0.13)	0.99 (0.08-8.62)
J17: Pneumonia in diseases classified elsewhere	1	0.01 (0.00-0.07)	1	0.02 (0.00-0.10)	1.48 (0.02-116.25)
J18: Pneumonia, organism unspecified	234	2.75 (2.41-3.13)	111	1.94 (1.59-2.33)	0.70 (0.56-0.88)

641      Table 3. Comparison of the number of hospitalizations and the incidence rates of  
 642      hospitalizations for individual ICD-10 diagnoses of the pneumonia diagnostic  
 643      group. Incidence rate ratios between the Vaccine eligible and Vaccine non-  
 644      eligible cohorts are shown.

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Birth-cohort	Length of stay (median days, IQR)	Proportion hospitalized (%)	Proportion admitted requiring ICU (%)
2005	4 (2-6)	21.3	1.2
2006	2 (1-4)	21.4	7.8
2007	2 (1-5)	13.4	3.3
2008	3 (2-4)	12.7	6.3
2009	3 (2-5)	12.4	12.1
2010	3 (2-4)	15.5	3.2
2011	3 (2-5)	18.8	5.0
2012	3 (2-6)	20.5	0
2013	4 (2-7)	18.4	10.6

647      Supplementary Table 1. Information regarding visits and admissions to The  
 648      Children's Hospital Iceland for treatment of paediatric pneumonia. Birth-cohorts  
 649      with full follow-up time are shown, 2005-2013.

## **Paper VI**



## **Introduction**

Pneumococcal conjugate vaccines (PCV) have been shown to provide direct protection against acute otitis media (AOM), pneumonia and invasive pneumococcal disease (IPD) in vaccinated individuals (Black et al. 2000; Cutts et al. 2005; Prymula et al. 2006; Tregnaghi et al. 2014). PCV can also provide indirect protection to unvaccinated members of the population, a process known as herd effect. The introduction of PCV into national paediatric immunization programmes has consistently been shown to result in indirect protection against IPD in unvaccinated children and adults (Shiri et al. 2017), and several observational studies have demonstrated indirect protection against pneumonia (Bruhn et al. 2017; Tsaban and Ben-Shimol 2017). However, indirect protection against AOM has been less well established (Ben-Shimol et al. 2014; Sigurdsson et al. 2018).

A plethora of cost-effectiveness analyses has been published examining the inclusion of PCV into national immunization programmes (Vooren et al. 2014). They have generally shown PCV to be a cost-effective intervention. However, most of the studies were conducted before the vaccine was implemented and their results were heavily dependent on assumptions regarding indirect protection (Holubar et al. 2017).

In 2011, the 10-valent pneumococcal *Haemophilus influenzae* Protein D conjugate vaccine (PHiD-CV, Synflorix) was included into the Icelandic paediatric immunization programme, with a two + one schedule given at three, five and 12 months of age. Children born in 2011 and later were eligible. Vaccine uptake was immediately high with over 97% of vaccine eligible children receiving the primary vaccination by their first birthday (Eythorasson et al. 2017).

The aim of the study was to evaluate the direct and indirect impact of introducing PHiD-CV10 on AOM, pneumonia and IPD in Iceland, and to perform a post-implementation cost-effectiveness analysis using directly observed data.

## **Methods**

### **Data sources**

The study was a population-based time series analysis. Data were obtained from the Primary Care Registry and National Drug Prescription Registry of the Icelandic Directorate of Health, and Landspítali University Hospital's patient registry. The Primary Care Registry contains information on all primary care visits in Iceland. Visits associated with International Classification of Diseases, 10th revision (ICD-10) diagnostic codes compatible with AOM and visits associated with chapters of the ICD-10 diagnostic coding system were extracted as synthetic controls (Table 1). The observation period was restricted to 1 January 2005 to 31 December 2015, as the Primary Care Registry was not updated for 2016 and 2017. All outpatient antimicrobial prescriptions were extracted from the National Drug Prescription Registry using Anatomical Therapeutic Chemical code J01 and linked to AOM visits through personal identification numbers. AOM visits associated with antimicrobial prescriptions were used as an alternate case-definition in sensitivity analyses.

Data regarding hospitalized pneumonia and IPD were obtained from Landspítali University Hospital's patient registry for the period 2005-2017. Hospitalized pneumonia was defined as any hospital admission associated with ICD-10 diagnostic codes compatible with pneumonia (Table 1). Hospitalized IPD was defined based on microbiological data, were extracted from a database maintained by the Department of Clinical Microbiology at Landspítali University Hospital and linked to the patient registry. Hospitalized IPD was defined as any hospital admission associated with culture or PCR-confirmed *Streptococcus pneumoniae* sampled from joint fluid, bone, cerebrospinal fluid or blood, regardless of ICD-10 discharge diagnosis. Hospitalizations associated with chapters of the ICD-10 diagnostic coding system were extracted as synthetic controls (Table 1).

Table 1 The International Classification of Diseases, 10th revision (ICD-10) codes used to define disease states and synthetic controls used in the time series analyses. Acute otitis media (AOM) and pneumonia were used as outcome measures and each given two alternate case-definitions that were used in sensitivity analyses along with urinary tract infections. Outpatient antimicrobial prescriptions were obtained from the National Drug Prescription Registry and linked to visits using national identification numbers. Inpatient microbiological and radiographical testing was ascertained through cost data. All other codes were used as synthetic controls. When applicable, codes associated with pneumococcal infections were excluded from control groupings.

Group	ICD-10	Description	Exclusions
Outcomes and alternatives	H65, H66, H70, H72	Acute otitis media	-
	H65, H66, H70, H72, and antimicrobial prescription	Acute otitis media (alternate)	-
	H66	Acute otitis media (alternate)	-
	J12, J13, J14, J15, J16, J17, J18	Pneumonia	-
	J13, J15.8, J15.9, J18.1, J18.8, J18.9	Pneumonia (alterante)	-
	J13, J15.8, J15.9, J18.1, J18.8, J18.9, and microbiological and radiographical testing	Pneumonia (alterante)	-
	Any or none	Positive pneumococcal culture or PCR from normally sterile site	-
	Any or none	Positive vaccine-type culture or PCR from normally sterile site (alterante)	-
	N10, N30.0, N39.0	Urinary tract infections (alterante)	-
ICD-10 chapters	A10-B99	Certain infectious and parasitic diseases	A40.3, B95
	C00-D48	Neoplasms	-
	D50-89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	-

E00-99	Endocrine, nutritional and metabolic diseases	-
G00-G99	Diseases of the nervous system	G00-G04
H00-99	Diseases of the eye and adnexa, Diseases of the ear and mastoid process	H10, H65, H66
I00-99	Diseases of the circulatory system	-
K00-99	Diseases of the digestive system	-
L00-99	Diseases of the skin and subcutaneous tissue	-
M00-99	Diseases of the musculoskeletal system and connective tissue	-
N00-99	Diseases of the genitourinary system	-
P00-99	Certain conditions originating in the perinatal period	-
Q00-99	Congenital malformations, deformations and chromosomal abnormalities	-
R00-99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	-
S00-T99	Provisional assignment of new diseases of uncertain etiology	-

	U00-99	Injury, poisoning and certain other consequences of external causes	-
	V00-Y99	External causes of morbidity	-
	Z00-99	Factors influencing health status and contact with health services	-
Other grouped and specific outcomes	J20-22	Bronchitis, bronchiolitis and unspecified acute lower respiratory infection	-
	B20-24	HIV	-
	E10-14	Diabetes	-
	I60-64	Stroke	-
	A09, K52.9, K59.1, R19.7	Gastroenteritis and Diarrhea	-
	P05-07	Premature delivery and low birth weight	-
	K35	Appendicitis	-
	K80	Cholelithiasis	-
	E86	Dehydration	-
	A00-Z99	All non-respiratory visits or hospitalizations	J00-J99, F and O chapters

For each hospitalization or emergency department visit, a detailed breakdown of cost was available, which was extracted for each of the disease categories included in the study. No cost data was available for primary care visits. Because Children's Hospital Iceland's paediatric emergency department serves as a walk-in clinic for the greater capital area, the distribution of costs for otitis media visits to the emergency department was assumed to mirror that of primary care visits, and was used in its stead. The number of PHiD-CV10 doses purchased by the government and the unit price for each dose per calendar year were obtained directly from the

Icelandic Directorate of Health. The yearly employment rate of individuals 15 to 24 years of age, 25 to 54 years of age and 55 to 64 years of age from 2011-2017 was extracted from Organization for Economic Cooperation and Development (OECD) Labour Force Statistics (*OECD Labour Force Statistics* 2018), and the deciles of regular total wage for working Icelanders from 2011-2017 were obtained from Statistics Iceland. The consumer price index for medical care obtained from Statistics Iceland was used to convert all direct health care costs to 2015 price levels in Icelandic kronas. All costs were converted to United States Dollars (USD) using the official exchange rates of the Icelandic Central Bank.

### **Impact of PHiD-CV10**

The impact of PHiD-CV10 introduction on the incidence of pneumococcal disease was estimated using time series methods and the result used as an input for a cost-effectiveness analysis. This was accomplished using a previously published Bayesian time series methodology (Bruhn et al. 2017; Shioda et al. 2018). The pre-vaccine period was defined as 1 January 2005 to 31 December 2010, and the post-vaccine period as 1 January 2013 to 31 December 2017. A transition period was included from 2011 to 2012. For each disease category and age-group, four models of PHiD-CV10 impact were estimated; an interrupted time series (ITS) with all non-respiratory visits or hospitalizations as an offset, ITS without offset, principal component analysis (Shioda et al. 2018), and a synthetic control model (Bruhn et al. 2017). All were Bayesian Poisson models with observation specific random intercepts to account for over-dispersion. Each model utilized the pre-vaccine period to predict the monthly occurrence of the outcome of interest in the post-vaccine period, had the vaccination not occurred. These models were then combined using a Bayesian model-stacking procedure (Vehtari et al. 2019). The methods are described in more detail in the supplementary appendix.

From the posterior predictive distribution of the stacked model, a total of 10,000 Markov chain Monte Carlo (MCMC) samples were drawn, representing the number of cases that would have occurred in the post-vaccine period, had the vaccine not been introduced. The first 2,000 MCMC draws were discarded for optimal burn-in. For each of the remaining 8,000 draws, the rate ratio between the observed and predicted number of cases during the post-vaccine period was calculated, and the median and 95% credible intervals extracted from the resulting distribution of rate ratios. To

estimate the onset of vaccine impact, the rate ratio was calculated over a rolling 12-month period, the first of which included 11-months of pre-vaccine data and one month of post-vaccine data. The number of cases prevented by the vaccine was calculated for each calendar-month, by subtracting the observed number of cases from each of the 8,000 MCMC draws. The cumulative sum of prevented cases was calculated, and the median and 95% credible intervals were extracted.

### **Cost-effectiveness analysis**

The cost-effectiveness of PHiD-CV10 introduction compared to no intervention was estimated from both the healthcare and societal perspectives using ecological post-implementation data. The societal perspective included both direct costs and indirect costs associated with productivity loss, while analysis from the health care perspective included only direct costs. Neither analysis included estimates of long-term sequelae or their associated costs. The time horizon was five years and both costs and cost-savings were discounted at a 3% discount rate. All costs were presented in constant 2015 USD. A summary of the cost-effectiveness parameters and assumptions are presented in Table 2.

Table 2 A summary of the parameters and assumptions of the cost-effectiveness analysis. All costs were first adjusted to constant 2015 values and converted to United States Dollars (USD). The cost of the vaccine, visits and hospitalizations were directly observed. The possible vaccine costs were assumed to follow a normal distribution with mean equal to the observed costs, and the standard deviation equal to 5 USD. The distribution of costs associated with visits and hospitalizations was empirically estimated using resampling with replacement. Wage and employment rates were obtained from Statistics Iceland. Wage was optimally fitted using a lognormal distribution as shown.

Parameter or Assumption	Description	Distribution
Perspective	Healthcare, Societal	-
Comparators	PHiD-CV10 vs no vaccine	-
Model	Ecological time series	-
Time horizon	5 years	-
Price date	2015	-

Discount rate	3%	$\sim \text{Triangle}(0, 6)$
Cost of vaccine	Directly observed	$\sim N(\text{observed}, 5 \text{ USD})$
Cost of visit or hospitalization	Directly observed	Resampling with replacement
Wage	Observed	$\sim \text{logN}(12.85, 0.35)$
Employment	Observed	$\sim \text{Binomial}(\text{observed})$
Days of work lost	Estimated from observed hospital length of stay	Resampling with replacement from hospital length of stay + $\sim \text{Pois}(1/2 \text{ hospital length of stay})$
Vaccine uptake	Implicitly included	-
Vaccine coverage	Implicitly included	-
Serotype replacement	Implicitly included	-
Herd-effect	Implicitly included	-

The direct cumulative savings associated with PHiD-CV10 introduction were calculated by multiplying the predicted number of prevented cases from the Bayesian time series analysis with the expected cost of each case. The expected cost was obtained through sampling with replacement from the observed costs extracted from Landspítali University Hospital's patient registry. The sampling was stratified by disease category and age-group. The direct costs associated with the introduction of PHiD-CV10 into the paediatric immunization programme were calculated for each calendar-year by multiplying the number of purchased doses by the price of each purchased dose. Wastage was taken into account, as this formula included doses that were for whatever reason never administered. Additional administration costs were however not assumed, as each dose was administered by nurses during the same visits that other established vaccines were being given. The direct costs associated with the vaccine were subtracted from the direct cumulative savings to obtain the final estimate of the total cost. This resulted in 8,000 posterior draws of the total cost, from which the median and 95% credible intervals were extracted.

Indirect costs due to productivity loss were accounted for in the analysis from the societal perspective. The deciles of wage that were extracted from Statistics Iceland were optimally fitted to a lognormal distribution to obtain a continuous distribution of wage (Belgorodski et al. 2017). The number of days

of work lost were assumed. For each case of otitis media in primary care, the days of work lost by a parent or guardian were assumed to follow a Poisson distribution with mean equaling one. For each pneumonia or invasive pneumococcal disease hospitalization, the days of work lost were assumed to equal the sum of the hospital length of stay and a variable time following discharge. For each prevented case, the associated hospital length of stay was sampled with replacement from the observed length of stay obtained from the patient registry. This variable time was assumed to be Poisson distributed with mean equal to half the observed hospital length of stay. The indirect costs were calculated by multiplying the days of work lost with wages sampled from the lognormal wage distribution, accounting for unemployment. Cost-effectiveness was summarized with incremental cost-effectiveness ratios (ICER) with 95% credible intervals.

### **Sensitivity analysis**

Sensitivity analyses were conducted for both the PHiD-CV10 impact models and the cost-effectiveness analysis. The Bayesian approach used to estimate the cost-effectiveness produces a posterior predictive distribution that includes the uncertainty associated with the input parameters. Four sensitivity analyses were performed to validate the robustness of the impact models.

Firstly, the sensitivity of the impact models to the choice of pre-vaccine period was evaluated by iteratively choosing three year pre-vaccine periods (2005-2007, 2006-2008, 2007-2009, and 2008-2010) and refitting the models for each disease category and age-group. Secondly, the robustness of the synthetic control models with regards to the included covariates was evaluated by removing the top covariate and re-estimating the rate ratio. This was done iteratively three times and the resulting three rate ratios were compared to the one obtained in the main analysis. Thirdly, several different case-definitions for each disease category were explored in separate sensitivity analyses. The models were refitted with two additional definitions of otitis media (visits with ICD-10 code H66 only, and visits with ICD-10 codes H65, H66, H70, H72, associated with a filled antimicrobial prescription), and two additional definitions of pneumonia (hospitalizations with ICD-10 codes J13, J15.8, J15.9, J18.1, J18.8 and J18.9; and hospitalizations with ICD-10 codes J13, J15.8, J15.9, J18.1, J18.8 and J18.9 in which microbiological and radiological examinations had been performed). The impact of PHiD-CV10 on vaccine-type IPD was also evaluated. Finally, the models were re-fitted with urinary tract infections as the outcome variable

to evaluate the specificity of the results with regard to infections likely to be caused by pneumococcus.

## Results

### **Population impact on acute otitis media among children younger than 20 years of age**

From 1 January 2005 to 31 December 2015, children younger than 20 years of age visited primary care physicians 164,453 times for AOM and its complications. The monthly number of AOM visits during the post-vaccine period was lower than average in all age-groups. Overall visits also decreased during the post-vaccine period, but the degree by which visits for AOM decreased was larger in magnitude (Supplementary Figure 1).

The posterior predicted AOM visits and 95% credible intervals are shown in Figure 1. With few exceptions, the observed number of AOM visits were fewer than predicted in the post-vaccine period, indicating that the vaccine prevented visits from occurring. The posterior predictions of each component model are shown in Supplementary Figure 2, and the weights used to produce the final stacked model are presented in Supplementary Table 1.

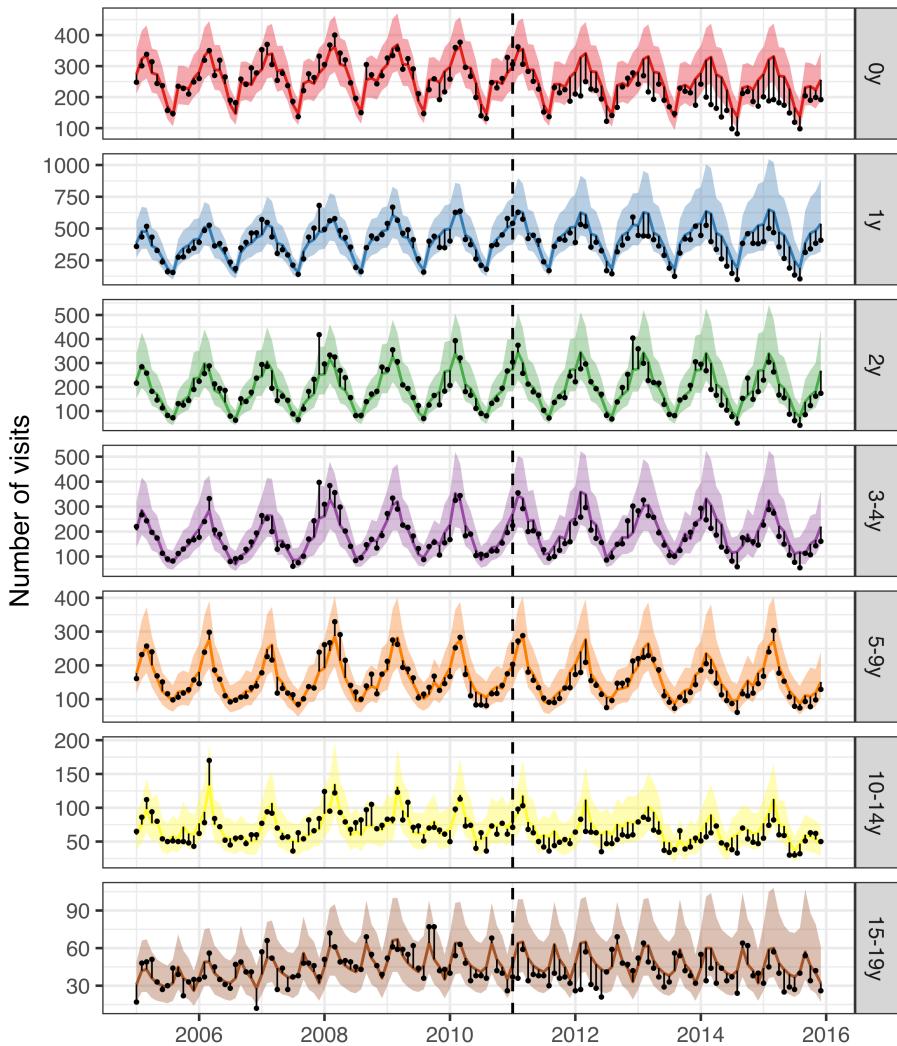


Figure 1 The observed and predicted number of AOM visits from 1 January 2005 to 31 December 2015 for each age-group. Observed visits are illustrated as black points, the posterior predicted visits are presented as lines and 95% credible intervals as a shaded area. The start of the vaccine period is delineated with a vertical black dotted line. The distance between the observed and predicted visits for each calendar-month is depicted with a thin black line. Assuming that the model is correct and that no intervention had taken place, the black points would have an equal probability of occurring above and below the prediction line. Points below the lower bound of the shaded area would then represent observations that would have had less than a 2.5% probability of occurring. Given that the majority of points are located below the prediction line, and many located below the lower bound of the shaded area, the figure suggests that the vaccine resulted in fewer AOM visits. Note that the scale of the Y-axis differ between age-groups.

The 95% credible interval of the rate ratio between the observed and predicted number of AOM visits was lower than one in all age-groups, indicating that there was a 97.5% or greater probability that the rate of AOM decreased due to the introduction of PHiD-CV10 in all age-groups (Table 3). The decrease was largest among young children; 16% (12%-36%) in children younger than one year of age and 18% (5%-42%) in children one year of age. A 12-month rolling rate ratio between the observed and predicted number of AOM cases is presented in Panel A of Figure 2. Visually, the rate of AOM cases among children younger than one seems to begin to decline in January 2012, and cases among children one year of age seems to decline in July 2012.

Table 3 The rate ratio between observed and predicted number of primary care visits due acute otitis media and complications (AOM) during the post-vaccine period (2013-2015), is presented with 95% credible intervals (95% CI) for the seven age-groups included in the study. The predicted cumulative number of prevented cases as of 1 December 2015 is also presented. A negative number indicates that there is a non-zero probability that the vaccine caused more AOM visits to occur. Direct and indirect savings are presented in 2015 USD.

Age-group	Rate ratio (95% CI)	Cumulative cases prevented (95% CI)	Direct savings (95% CI)	Indirect savings (95% CI)
0y	0.74 (0.64- 0.88)	3,234 (1,008 to 5,195)	305,330\$ (90,933\$ to 514,848\$)	45,386\$ (11,143\$ to 84,654\$)
1y	0.72 (0.58- 0.95)	5,802 (817 to 11,526)	530,468\$ (57,564\$ to 1,150,759\$)	74,298\$ (3,778\$ to 193,180\$)
2y	0.88 (0.66- 0.98)	900 (-185 to 3,817)	92,117\$ (- 52,649\$ to 407,227\$)	14,377\$ (- 11,004\$ to 64,562\$)
3-4y	0.86 (0.69- 0.97)	1,702 (21 to 3,576)	135,274\$ (- 16,985\$ to 357,905\$)	23,880\$ (- 4,324\$ to 62,811\$)
5-9y	0.88 (0.73- 0.96)	979 (229 to 2,521)	134,548\$ (- 38,612\$ to 430,729\$)	14,242\$ (- 1,030\$ to 40,961\$)

10-14y	0.83 (0.75- 0.92)	720 (411 to 1,086)	113,333\$ (4,669\$ to 285,816\$)	10,313\$ (- 3,098\$ to 20,035\$)
15-19y	0.89 (0.56- 0.98)	430 (210 to 1,689)	55,819\$ (-8,278\$ to 227,493\$)	6,169\$ (698\$ to 25,248\$)

The cumulative number of prevented AOM cases reflect both the rate of AOM cases in each age-group, and the consistency and magnitude of the vaccine effect. The cumulative prevented cases per age-group as of December 2015 are presented in Table 3. The largest effects are seen in the youngest age-groups, who both had the highest baseline rates and experienced the largest relative declines following vaccine introduction. The cumulative number of prevented cases as a function of time during the post-vaccine period is shown in Panel B of Figure 2.

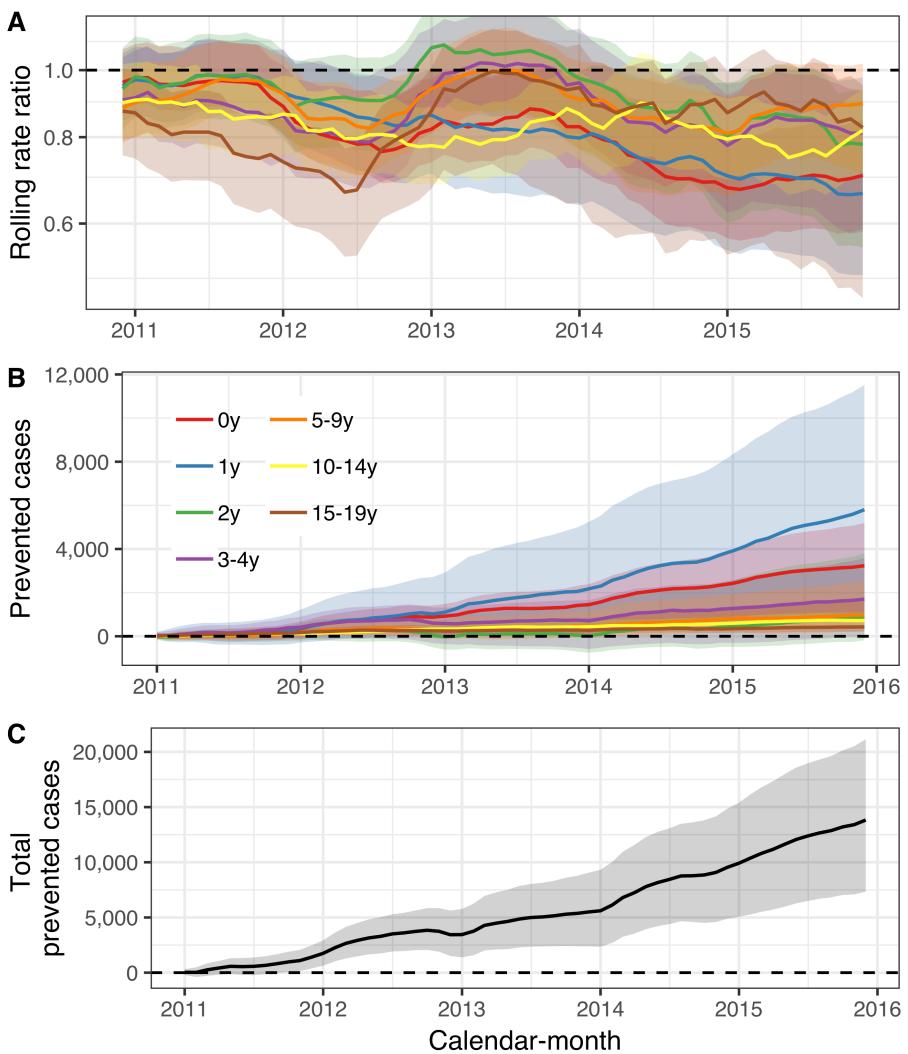


Figure 2 The impact of the 10-valent *Haemophilus influenzae* protein D pneumococcal conjugate vaccine (PHiD-CV10) on acute otitis media and complications (AOM) among children younger than 20 years of age is summarized. In Panel A, the estimated 12-month rolling rate ratio between observed and predicted AOM cases is shown per age-group, and the 95% credible intervals (CI) are illustrated as a shaded area. Panel B depicts the cumulative number of prevented AOM cases during the post-vaccine period (2011-2015) for each age-group, along with 95% CI. The total cumulative prevented AOM cases regardless of age-group is shown in Panel C.

Sensitivity analyses did not reveal important inconsistencies regarding the underlying modeling assumptions. The result was invariant to different case-definitions, the inclusion of different controls and different pre-vaccine

periods. Additionally, the time series framework did not predict a decrease in urinary tract infections (Supplementary appendix).

### **Population impact on pneumonia hospitalizations**

From 1 January 2005 to 31 December 2017, 13,373 hospitalizations for pneumonia were recorded. Monthly pneumonia hospitalizations displayed complex trends over the study period. Pneumonia hospitalizations increased fairly rapidly during the pre-vaccine period among adults 40 years and older, and subsequently decreased at variable times in the post-vaccine period. Similarly, hospitalizations regardless of diagnosis increased among adults 20 years and older during the pre-vaccine period (Supplementary Figure 3).

The predicted number of cases and 95% credible intervals are shown in Figure 3. During most of the post-vaccine period, the observed number of hospitalizations were equal to or below the prediction line among children zero to four years of age, and among adults 20 to 39, 65-79 and 80 years of age and older. The posterior predictions of the component models are shown in Supplementary Figure 4 and the weights used to produce the final stacked model are presented in Supplementary Table 1.

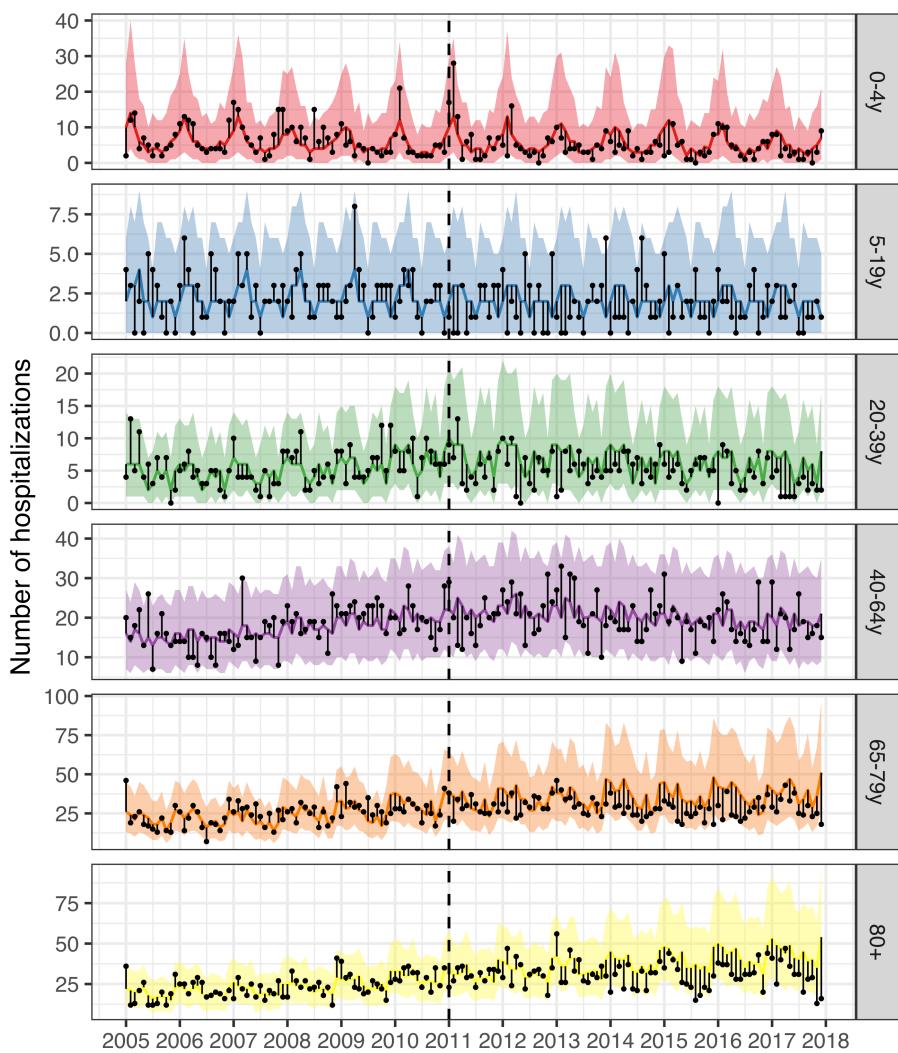


Figure 3 The observed and predicted number of pneumonia hospitalizations from 1 January 2005 to 31 December 2017 for each age-group. Observed cases are illustrated as black points. The predicted number of hospitalizations are presented as lines and 95% credible intervals as a shaded area. The start of the vaccine period is delineated with a vertical black dotted line. The distance between the observed and predicted cases for each calendar-month is depicted with a thin black line. Assuming that the model is correct and that no intervention had occurred, the black points would have an equal probability of appearing above and below the prediction line. Given that the majority of points are located below the prediction line, the figure suggests that the vaccine resulted in fewer pneumonia hospitalizations. Note that the scale of the Y-axis differ between age-groups.

The rate ratios between the observed and predicted number of pneumonia hospitalizations are shown in Table 4. Among children zero to four years of age, the posterior median of the rate ratio was 0.67, and the 2.5% credible limit was 0.51. This was consistent with a 2.5% probability that the rate ratio was lower than 0.51 and a 47.5% probability that the rate ratio laid between 0.51 and 0.67. Though the 97.5% credible limit was above the threshold value of one, there was a 94% probability that the rate ratio was lower than one, and a 90% probability that it was lower than 0.83. Similarly the posterior median of the rate ratio was 0.74 among children five to 19 years of age, and there was a 90% probability that the rate ratio was lower than one. Among adults 65 to 79 years of age, and 80 years of age and older, the posterior median of the rate ratio was 0.75 and 0.76 respectively, and both had a 97% probability of being lower than one.

A 12-month rolling rate ratio between the observed and predicted number pneumonia hospitalizations is presented in Panel A of Figure 4. Visually, the rate of pneumonia hospitalizations among children zero to four years of age seems to begin to decline in January 2012 (the first rolling 12-month period to include only post-vaccine months), and hospitalizations among adults 65 years of age and older seems to begin to decline in January 2014.

Table 4 The posterior median of the rate ratio between observed and predicted number pneumonia hospitalizations during the post-vaccine period (2013-2017) is presented with 95% credible intervals (95% CI) for the six age-groups included in the study. The predicted cumulative number of prevented cases as of 1 December 2017 is also presented. A negative number indicates that there is a non-zero probability that the vaccine caused more pneumonia hospitalizations to occur. Direct and indirect savings are presented in 2015 USD.

Age-group	Rate ratio (95% CI)	Cumulative cases prevented (95% CI)	Direct savings (95% CI)	Indirect savings (95% CI)
0-4y	0.67 (0.51- 1.39)	142 (-115 to 307)	444,533\$ (- 44,181\$ to 1,309,917\$)	52,535\$ (- 59,043\$ to 136,715\$)
5-19y	0.74 (0.54- 1.35)	52 (-27 to 113)	234,848\$ (- 236,236\$ to 748,522\$)	20,472\$ (- 18,876\$ to 61,481\$)
20-39y	0.68 (0.51- 0.95)	182 (14 to 384)	968,662\$ (- 203,048\$ to 2,567,059\$)	70,071\$ (- 9,442\$ to 164,747\$)

40- 64y	0.92 (0.79- 1.22)	141 (-270 to 445)	933,290\$ (- 2,748,49\$ to 4,848,557\$)	71,953\$ (- 113,414\$ to 223,171\$)
65- 79y	0.75 (0.55- 1.02)	666 (-49 to 1,648)	5,476,585\$ (- 910,021\$ to 15,590,280\$)	323,964\$ (- 4,745\$ to 786,252\$)
80+	0.76 (0.56- 1.02)	631 (-76 to 1,615)	4,664,256\$ (- 817,266\$ to 13,013,699\$)	287,270\$ (- 37,961\$ to 742,168\$)

The cumulative prevented pneumonia hospitalizations per age-group as of December 2017 are presented in Table 4. The largest effects were seen in adults 65 years of age and older, which reflects the baseline number of cases. The predicted cumulative number of prevented hospitalizations as a function of time during the post-vaccine period is shown in Panel B of Figure 4.

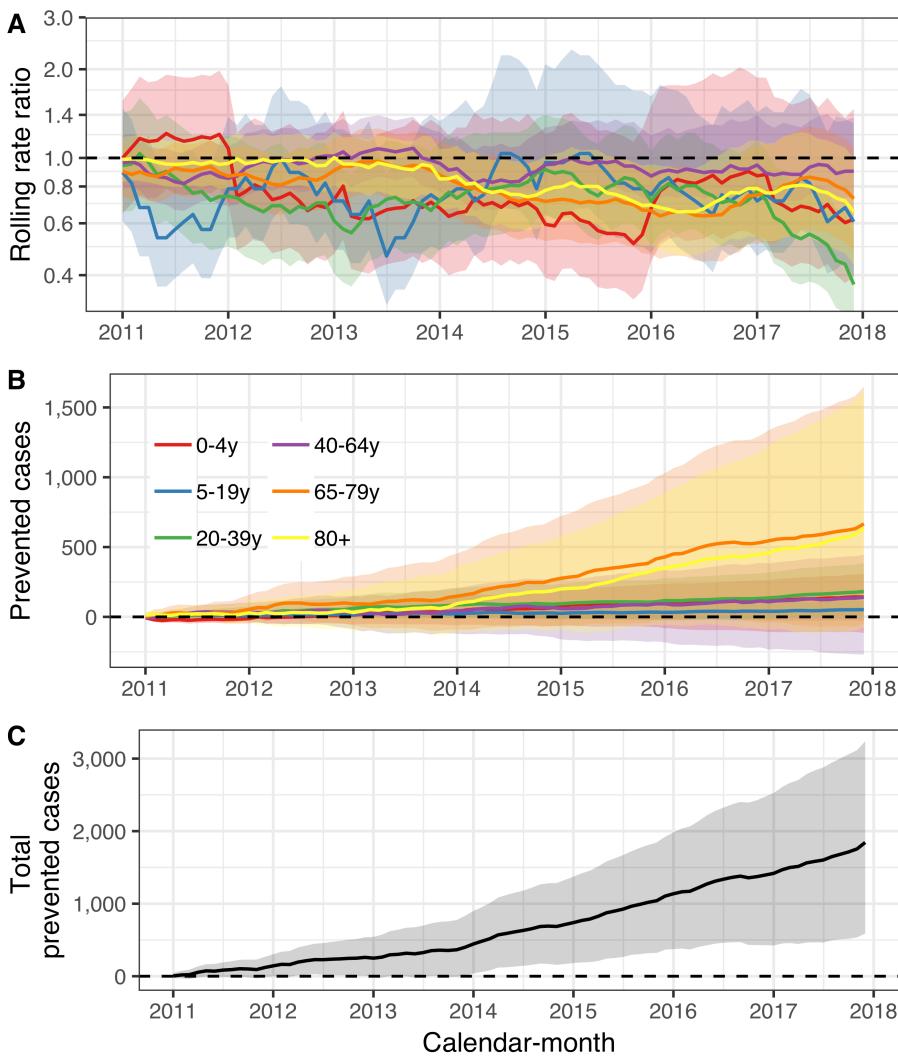


Figure 4 The population impact of the 10-valent *Haemophilus influenzae* protein D pneumococcal conjugate vaccine (PHiD-CV10) on pneumonia hospitalizations is summarized. In Panel A, the estimated 12-month rolling rate ratio between observed and predicted pneumonia hospitalizations is shown per age-group, and the 95% credible intervals (CI) are illustrated as a shaded area. Panel B depicts the cumulative number of prevented pneumonia hospitalizations during the post-vaccine period (2011-2017) for each age-group along with 95% CI. The total cumulative prevented pneumonia hospitalizations regardless of age-group is shown in Panel C.

Sensitivity analysis revealed that stricter definitions of pneumonia resulted in more significant declines than the base-case analysis. Some component models became unstable when only three years (2005-2007) of pre-vaccine

data were used to fit them. The time series methodology did not predict a decrease in urinary tract infections (Supplementary appendix).

### **Population impact on hospital admissions for invasive pneumococcal disease**

From 1 January 2005 to 31 December 2016, 338 hospitalizations for culture confirmed invasive pneumococcal disease were recorded. Of those, 206 occurred before the introduction of PHiD-CV10 into the paediatric immunization programme in Iceland. Standardized hospitalizations for IPD decreased among children zero to four years of age, while standardized hospital admissions regardless of cause did not decrease to the same extent (Supplementary Figure 5). Discrepancies between hospital admissions for IPD and all-cause hospitalizations were also noted in the other age-groups. Hospitalizations for IPD among individuals five to 64 years of age decreased while all-cause hospitalizations remained stable. While hospital admissions for IPD among adults 65 years of age and older did not change visibly, the standardized all-cause hospitalizations increased, suggesting a relative decline in IPD admissions (Supplementary Figure 5).

The posterior prediction of IPD hospitalizations and 95% credible intervals are shown in Figure 5. Among children zero to four years of age, observed IPD hospitalizations were equal to or fewer than the predicted hospitalizations in all but two quarters. Similarly, observed hospitalizations among individuals five to 64 years of age were fewer than predicted more often than expected. Both suggest that the vaccine prevented cases from occurring. The posterior predictions of the component models are shown in Supplementary Figure 5 and the stacking weights are shown in Supplementary Table 1.

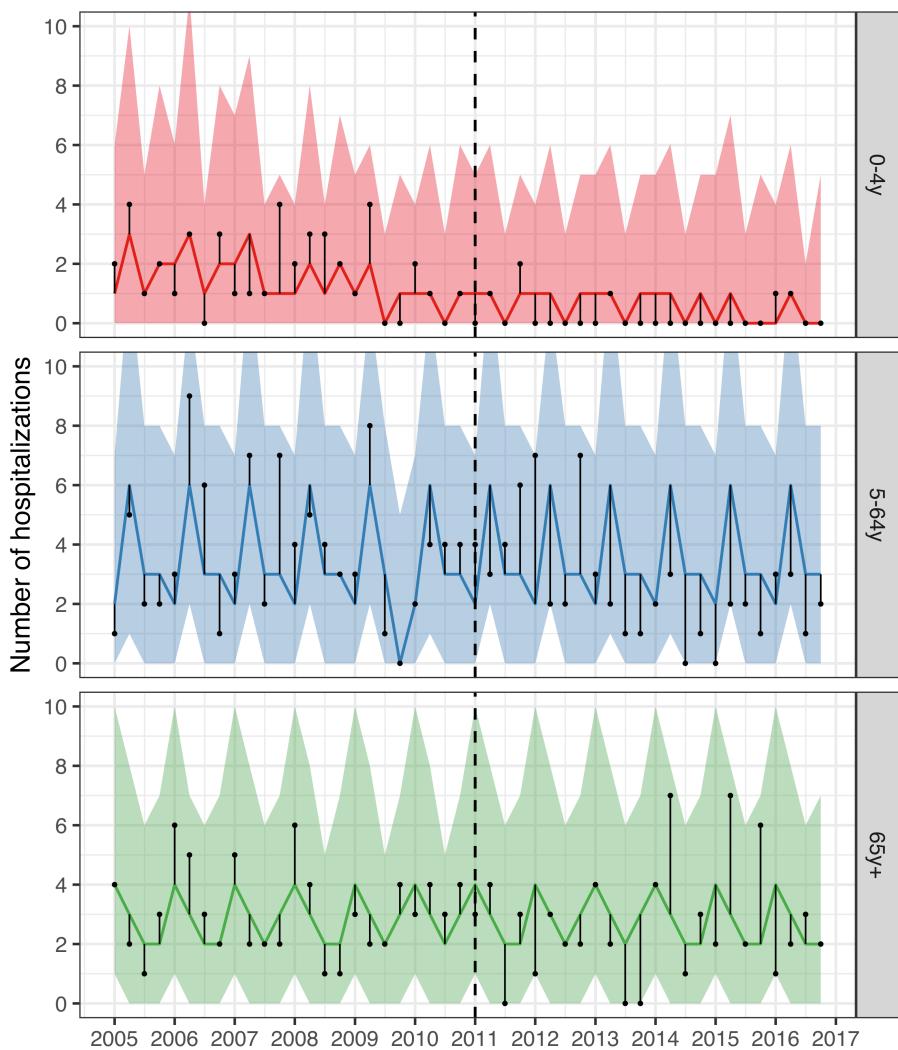


Figure 5 The observed and predicted number of IPD hospitalizations from 1 January 2005 to 31 December 2016 for each age-group. Observed cases are illustrated as black points, and the predicted number of cases are presented as lines with 95% credible intervals as a shaded area. The start of the vaccine period is delineated with a vertical black dotted line. The distance between the observed and predicted cases for each year-quarter is depicted with a thin black line. Assuming that the model is correct and no intervention had taken place, the black points would have an equal probability of occurring above and below the prediction line. Given that the majority of points are located below the prediction line, the figure suggests that the vaccine resulted in fewer IPD hospitalizations.

The rate ratios between the observed and predicted number of IPD hospitalizations in the post-vaccine period are shown in Table 5. The

posterior median of the rate ratio for children younger than five years of age was 0.27, corresponding to a 50% probability that the vaccine impact was greater than or equal to 73%. The 95% credible intervals of the rate ratio were wide, reflecting the uncertainty due to the few number of IPD hospitalizations. However, 90% of the MCMC draws of the rate ratio were below 0.75 and 93% were under the threshold value of one. The 95% credible interval of the rate ratio among individuals five to 64 years of age was lower than one, indicating a 97.5% or greater probability that the rate of IPD hospitalization decreased in this age-group following the introduction of PHiD-CV10.

The 12-month rolling rate ratio is presented in Panel A of Figure 6. The rolling rate ratio for children zero to four years of age was unstable due to numerical issues with both the numerator and the denominator. In some 12-month periods, no IPD hospitalizations were observed and the resulting rate ratio was zero regardless of the denominator. In other periods, 2.5% or more of the MCMC draws predicted zero IPD hospitalizations, which resulted in a 95% credible intervals of the rate ratio that extended towards infinity. These issues do not change the overall interpretation of the prediction line presented in Panel A of Figure 6.

Table 5 The rate ratio between observed and predicted number of hospital admissions for invasive pneumococcal disease (IPD) during the post-vaccine period (2013-2016) is presented along with 95% credible intervals (95% CI) for the three age-groups. The predicted cumulative number of prevented cases as of 1 December 2016 is also presented. A negative number indicates that there is a non-zero probability that the vaccine caused more IPD hospitalizations to occur. Direct and indirect savings are presented in 2015 USD.

Age-group	Rate ratio (95% CI)	Cumulative cases prevented (95% CI)	Direct savings (95% CI)	Indirect savings (95% CI)
0-4y	0.27 (0.05- 3.00)	14 (-2 to 67)	227,087\$ (71,363\$ to 618,919\$)	16,882\$ (6,893\$ to 38,718\$)
5-64y	0.44 (0.31- 0.68)	29 (1 to 65)	321,424\$ (- 455,573\$ to 1,649,171\$)	12,983\$ (- 3,606\$ to 33,498\$)
65y+	0.94 (0.62- 1.53)	10 (-16 to 45)	73,395\$ (- 256,856\$ to 516,864\$)	4,340\$ (- 10,903\$ to 23,543\$)

The cumulative prevented IPD hospitalizations per age-group as of December 2016 are presented Table 5, and are shown as a function of time in Panel B of Figure 6. The posterior median of the cumulative prevented cases increases from the beginning of the post-vaccine period among children zero to four years of age.

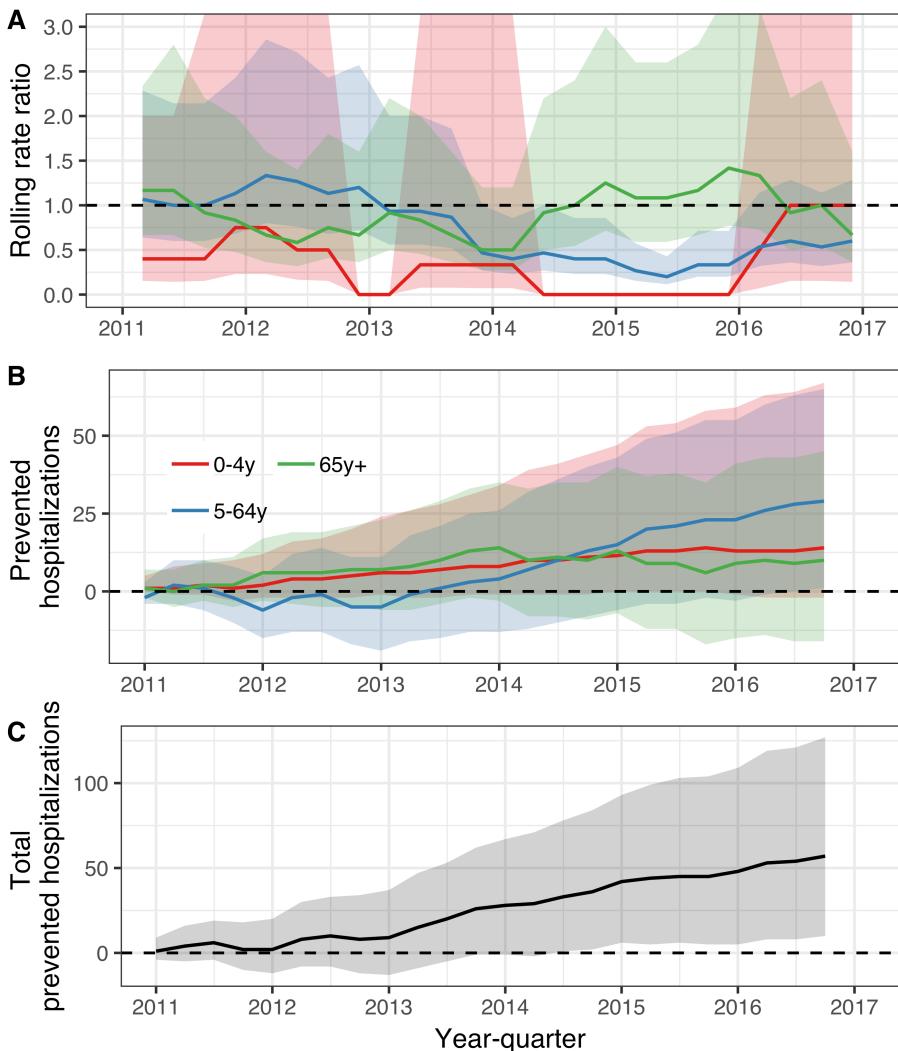


Figure 6 The population impact of the 10-valent *Haemophilus influenzae* protein D pneumococcal conjugate vaccine (PHiD-CV10) on hospital admissions for invasive pneumococcal disease is summarized. In Panel A, the estimated 12-month rolling rate ratio between the observed and predicted number of IPD hospitalizations in the post-vaccine period (2011-2016) is shown per age-group. Panel B depicts the cumulative number of prevented IPD hospitalizations during the post-vaccine period (2011-2015)

for each age-group along with 95% credible intervals. The total cumulative prevented IPD hospitalizations regardless of age-group is shown in Panel C.

Sensitivity analyses using restricted pre-vaccine periods were not possible as the models did not fit with such small amount of data. The results did not change with the inclusion of different controls (supplementary appendix).

### **Cost-effectiveness of PHiD-CV10**

The total cost of introducing PHiD-CV10 into the Icelandic paediatric immunization programme from 1 January 2011 to 31 December 2017 was 3,451,805\$ in constant 2015 USD. When direct cost-savings due to reductions in primary care visits for AOM, and hospital admissions for pneumonia and invasive pneumococcal disease were included, the cost of the PHiD-CV10 introduction was -7,463,176\$ (95% credible intervals -16,159,551\$ to -582,135\$) from the healthcare perspective as of 31 December 2015. This means that the immunization programme was cost-saving by 7,463,176\$. Including days of work lost, the total cost of including PHiD-CV10 in the paediatric immunization programme from the societal perspective was -8,164,894\$ (95% credible interval -17,197,959\$ to -1,004,553\$) as of 31 December 2015.

Given the observed distribution of costs associated with each AOM visit, the direct savings resulting from vaccine-prevented AOM visits was 1,389,900\$ (95% credible interval 704,319\$ to 2,201,925\$). The vaccine introduction prevented 10,911 days of work lost due to AOM (95% credible interval 5,116 to 18,801), which translated to 194,152\$ (95% credible interval 78,200\$ to 364,155\$) in productivity gains. The direct and indirect savings resulting from prevented AOM visits are shown in Table 3. Including only direct costs from averted visits and hospitalizations, the ICER was -543\$ (95% credible interval -1,508\$ to -48\$) per prevented AOM case from the healthcare perspective. The corresponding ICER including indirect costs was -594\$ (95% credible interval -1,597\$ to -76\$) per AOM case prevented.

The direct savings resulting from vaccine-prevented pneumonia hospitalizations was 13,330,902\$ (95% credible interval 2,933,955\$ to 26,270,332\$), given the observed distribution of costs associated with each hospitalization. If the vaccine is assumed to have no other benefits than preventing pneumonia hospitalizations, and only the direct costs are considered, the ICER was -5,315\$ (95% credible interval -8,877\$ to 711\$) per prevented pneumonia hospitalization, indicating a net savings of 5,315\$

for each prevented hospitalization from the healthcare perspective. The immunization programme prevented 29,969 days of work lost (95% credible interval 9,964 to 52,900), which translated to 838,952\$ (95% credible interval 273,559\$ to 1,493,478\$) in productivity gains. The direct and indirect savings resulting from prevented pneumonia hospitalizations are shown in Table 4. When cost-savings due to reductions in AOM visits or hospital admissions for IPD were also included, the ICER per prevented pneumonia hospitalization - 5,640\$ (95% credible interval -10,336\$ to -1,032\$) from the healthcare perspective as of 31 December 2015. Additionally including loss of work resulted in an ICER of -7,440\$ (95% credible interval -13,701\$ to -1,175\$).

The direct savings resulting from vaccine-prevented hospitalizations of IPD was 673,008\$ (95% credible intervals -189,654\$ to 2,081,594\$). The vaccine introduction prevented 1,280 days of work lost (444 to 2,410) due to IPD, which translated to 35,280\$ (95% credible intervals 9,437\$ to 70,609\$) in productivity gains. The direct and indirect savings resulting from prevented hospitalizations for IPD are shown in Table 4. When cost-savings due to reductions in AOM visits or hospital admissions for pneumonia were also included, the ICER was -119,992\$ (95% credible interval -387,183\$ to -9,542\$) per prevented IPD hospitalization from the health care perspective. When days of work lost were also considered, the ICER was -130,791\$ (95% credible interval -416,004\$ to -15,860\$) per prevented IPD hospitalization.

## **Discussion**

This population-based time series analysis demonstrated a direct and indirect impact of PHiD-CV10 introduction on AOM, pneumonia and IPD in Iceland. The results were robust to sensitivity analyses, which did not reveal evidence of significant confounding, and some scenarios showing a larger effect than the base analysis. After considering savings due to prevented episodes of pneumococcal infections, the PHiD-CV10 programme was shown to be cost-saving from both the healthcare and societal perspectives.

The study is strengthened by its long observation period and the completeness of the underlying data. Six years of pre-vaccine data were available and were used to estimate secular trends occurring before the implementation of the vaccine. Between five and seven years of post-implementation data were included depending on the outcome being considered. Both periods are longer than most previous observational studies of PCV impact (Bruhn et al. 2017; Tsaban and Ben-Shimol 2017).

The underlying population-based data is of high quality. All primary care centers use the same electronic medical record system and the same ICD-10 diagnostic coding system as Landspítali University Hospital and Children's Hospital Iceland, and both systems have been in exclusive use during the entire study period. The Primary Care Registry of the Icelandic Directorate of Health contains data on all primary care contacts in the country. Though Landspítali University Hospital is a single center, it is the sole tertiary hospital in Iceland, and includes Children's Hospital Iceland – Iceland's only pediatric hospital. It provides primary and secondary care for the capital area, approximately 65% of the Icelandic population, and tertiary care for the whole population. In 2017, the total number of non-psychiatric curative care hospital beds in Iceland was 732 ([www.statice.is](http://www.statice.is)). Of those, 669 (91%) were at Landspítali University Hospital.

### **Direct and indirect impact of PHiD-CV10 on acute otitis media**

We estimated the vaccine impact separately for children younger than one, one, two, three to four, five to nine, 10-14 and 15-19 years of age, and demonstrated a large direct and indirect impact. The direct impact was 26% among children younger than one year of age, 28% among one year olds, 12% among two year olds and 14% among children three to four years of age. The indirect impact was 12%, 17% and 11% in children five to nine, 10-14 and 15-19 years of age respectively. For these estimates, the 95% credible intervals did not cross the ratio value of one, which translates to a 97.5% or higher probability that the impact was larger than or equal to 1%.

Two systematic reviews of the impact of PCV on AOM have been published (Taylor et al. 2012; Vojtek, Nordgren, and Hoet 2017). Of the nine observational studies that evaluated the impact of PCV on otitis media, only three adjusted for secular trends (Grijalva et al. 2006; Lau et al. 2015; Marom et al. 2014). Lau et al. (2015) used an interrupted time series approach to estimate the sequential impact of PCV7 and PCV13 on otitis media in general practice, and reported a 21.8% reduction in the rate of otitis media visits in children younger than 10 years of age. Marom et al. (2014) and Grijalva et al. (2006) calculated rate ratios of otitis media visits between children younger than two years of age and children three to six years of age, and estimated the impact to be 20% and 27% respectively. Only two previous studies have suggested indirect protection of PCV against AOM (Ben-Shimol et al. 2014; Sigurdsson et al. 2018). Both reported fewer episodes among children younger than four months of age,

who were too young to have received direct protection from PCV. Ben-Shimol et al. (2014) described a decrease in positive pneumococcal cultures from samples taken from the middle ear of children in this age-group, and Sigurdsson et al. (2018) noted fewer primary care diagnosed AOM episodes.

Our study builds upon the literature by providing population-based estimates of direct and indirect PCV impact on AOM that is adjusted for several controls and for secular trends. Furthermore, extensive sensitivity analyses demonstrated that the result was robust to different case definitions of AOM, and that no spurious decline was observed in urinary tract infections.

### **Direct and indirect impact of PHiD-CV10 on pneumonia**

We demonstrated a 33% impact on hospitalized pneumonia among children zero to four years of age. Though the 97.5% credible limit was below the threshold value of 0%, the data was consistent with a 94% probability that the impact was larger than 1%, and a 90% probability that the impact was larger than 17%. The cumulative number of prevented hospital admissions for pneumonia in this age-group during the first seven years of the post-vaccine period was 142 (95% credible intervals -115 to 307) – an impressive decline considering that the baseline rate of pneumonia hospitalization was 65-75 per year in this age-group. The indirect impact on pneumonia hospitalizations in children five to 19 years of age was 26%, and was 32% among adults 20-39 years of age, 25% among adults 65-79 years of age and 24% among adults 80 years of age and older. Additionally, our data was consistent with a 8% impact among adults 40-64 years of age with a 77.5% probability that the impact was equal to or larger than 1%. The posterior estimate of impact for children five to 19 years of age was compatible with a 90% probability that the impact was equal to or larger than 1%.

According to a recent systematic review and meta-analysis, the average direct vaccine impact on clinical pneumonia was 17% (95%CI 11% to 22%) (Alicino et al. 2017). Of the observational studies identified by the systematic review, three were population-based (Berglund et al. 2014; Nair et al. 2016; Saxena et al. 2015). Only two of identified studies discussed or attempted to adjust for secular trends (Sgambatti et al. 2016; Simonsen et al. 2014). The methods used in our study are based on Bruhn et al. (2017), who demonstrated their method using data on pneumonia hospitalizations in five countries; Brazil, Chile, Ecuador, Mexico and the United States, before and after the introduction of PCV7 and PHiD-CV10 and showed a 14% to 45%

impact on pneumonia hospitalizations among children younger than 12 months of age.

To our knowledge, only seven previous publications have examined the indirect impact of pneumococcal conjugate vaccines on pneumonia hospitalizations among the unvaccinated population (Andrade et al. 2017; Bruhn et al. 2017; Griffin et al. 2013; Grijalva et al. 2007; Jardine, Menzies, and McIntyre 2010; Simonsen et al. 2011, 2014), five of which were identified by a recent systematic review (Tsaban and Ben-Shimol 2017). Two of the included studies, Simonsen et al. (2011) and Griffin et al. (2013), did not adjust for secular trends. The results of the remaining five publications generally showed a reduction in the incidence of pneumonia hospitalizations in children five to 17 years of age, and among adults 18-39 and 40-64 years of age, though the exact bounds of the age-groups and point-estimates varied between studies. Impact estimates ranged from 3% to 24% among children five to 17 years of age; 0% to 26% among adults 18-39 years of age; and 0% to 19% among adults 40-64 years of age (Andrade et al. 2017; Bruhn et al. 2017; Griffin et al. 2013; Grijalva et al. 2007; Jardine, Menzies, and McIntyre 2010; Simonsen et al. 2011, 2014). All but two of the studies suggested an impact among adults 65 years of age and older, with estimates ranging from 3% to 15%, though none reached significance at the pre-specified alpha of 0.05. Bruhn et al. (2017) reported the impact of PCV on pneumonia hospitalizations in five countries and divided the oldest age-group into adults 65-79 years of age and adults 80 years of age and older, as do we. Using a sophisticated synthetic-control methodology, they did not find evidence of impact among these age-groups.

Our findings of herd-effect among adults older than 65 years of age are discordant with Bruhn et al. (2017) – a publication that describes the methods employed in our study. There are several possible reasons for this disagreement. Our study examined the impact of PHiD-CV10, while theirs was primarily a study of PCV7. In Iceland, the uptake of PHiD-CV10 was immediately high, achieving over 97% uptake of the primary doses among vaccine eligible children (Eythorsson et al. 2017). Contrast this with the United States where uptake of two primary doses was initially 18% in 2002 and increased to 46% in 2004 (McLaughlin et al. 2016). For the other countries included in Bruhn et al. (2017), uptake for three doses during the first year of PCV introduction was 9% in Mexico, 17% in Ecuador, 55% in Chile, and 82% in Brazil (Oliveira et al. 2016). We included seven years of data following vaccine introduction, compared to two to five years of post-

vaccine data in Bruhn et al. (2017), which may have been needed for the indirect impact to present itself.

Our results were consistent with a large direct and indirect impact on pneumonia hospitalizations. Sensitivity analyses revealed the result to be robust with regards to different case definitions, controls and pre-vaccine periods.

### **Direct and indirect impact of PHiD-CV10 on invasive pneumococcal disease**

We demonstrated that among individuals five to 64 years of age, the introduction of PHiD-CV10 prevented 29 (95% credible interval 1 to 65) cases of IPD serious enough to warrant hospital admission in the first seven years of the immunization program. Before the vaccine introduction, this population experienced 16 IPD hospitalizations per year. The rate ratio between the observed and predicted number of IPD hospitalizations was 0.44 (95% credible intervals 0.31-0.68), which translates to a 56% vaccine impact in this age-group and is compatible with a 99% probability that the impact is equal to or larger than 1%. Examination of the rolling rate ratio presented in Figure 6, shows that impact was first detectable in the latter half of 2013, and achieved a 50% reduction in the beginning of 2014. Conversely, the evidence of herd-effect among adults 65 years of age and older was less clear. The cumulative number of prevented cases were 10 (95% credible intervals -16 to 45) and rate ratio was 0.94 (95% credible intervals 0.62-1.53), which is consistent with a 50% probability that the vaccine impact was 6% or larger in this age-group, and a 62.5% probability that the impact was equal to or larger than 1%. The rolling rate ratio presented in Figure 6 did not suggest an evolving trend towards an observable impact.

Two systematic reviews identified 262 observational studies published between 1 January 1994 and 6 January 2016 that examined the direct and indirect impact of PCV on vaccine-type and all-cause IPD (Davis et al. 2013; Shiri et al. 2017). The publication by Shiri et al. (2017) was also a meta-analysis, which used a Bayesian mixed-effects model to translate the included studies into a single estimate. The study demonstrated a yearly post-vaccine risk ratio of vaccine-type IPD of 0.79 (95% credible intervals 0.75-0.81), translating to a mean period to attain a 50% population reduction of vaccine-type IPD of 2.3 years (95% credible interval 1.9-2.7), and 8.9 years (95% credible interval 7.8-10.3) to attain a 90% reduction (Shiri et al. 2017). When stratified by age-group, the yearly risk ratio of vaccine-type IPD

was 0.77 among adults 65 years of age and older, and the time until 50% and 90% reduction was 4.1 and 10.3 years respectively. Interestingly, the results for IPD regardless of serotype were different. The yearly risk ratio for all age-groups was 0.99 (95% credible intervals 0.96-0.99) and the time until 50% and 90% reduction were not estimated. When stratified by age-group, the mean predicted reduction of all-cause IPD among adults 65 years of age and older was only 30% (Shiri et al. 2017).

Our findings are largely congruent with previous studies examining the herd-effect of PCV on all-cause IPD. We show a robust indirect protection among individuals five to 64 years of age, after adjusting for any secular trends in the pre-vaccine period, and the result is consistent with visual examination of the raw data (Figure 6). This is an important finding for policy decisions, as this age-group represents the population of working adults in any given country. Though our findings are consistent with slight decrease in IPD hospitalizations among adults 65 and older, the effect is not as obvious. While surprising, this result is consistent with the body of literature which seems to suggest a large and robust impact on vaccine-type IPD in this age-group, but a marginal impact on all-cause IPD (Davis et al. 2013; Shiri et al. 2017). Sensitivity analyses with regards to the inclusion of different controls did change the overall results.

### **Cost-effectiveness of PHiD-CV10**

Our results showed that the introduction of PHiD-CV10 was cost-saving by 7,463,176\$ in constant 2015 USD from the health care perspective. The direct cost of introducing the vaccine was 2,652,364\$ as of 31 December 2015. However, this cost was offset by the cost-savings associated with averted otitis media visits, pneumonia admissions and hospitalized IPD, which totaled 10,115,540\$. When the societal perspective was considered, and averted lost workdays were also included, the vaccine introduction was cost-saving by 8,164,894\$. The direct savings resulting from vaccine-prevented cases of AOM was 1,389,900\$. The incremental cost-effectiveness ratio per prevented case of AOM was -543\$ (95% credible interval -1,508\$ to -48\$) – that is, the health care system's monetary gains exceeded the initial expenditure, resulting in each additional case averted saving rather than costing money. Similar numbers were seen for hospitalized disease. The ICER for each additional prevented pneumonia hospitalization was -5,640\$ (95% credible interval -10,336\$ to -1,032\$) and -

119,992\$ (95% credible interval -387,183\$ to -9,542\$) per prevented IPD hospitalization.

A large number of cost-effectiveness analyses of pneumococcal conjugate vaccines have previously been published (Saokaew et al. 2016; Vooren et al. 2014; Wu et al. 2015). Of those, 21 studies examined the cost-effectiveness of PHiD-CV10 or PCV13 (Blank and Szucs 2012; By et al. 2012; Castiglia et al. 2017; Chuck et al. 2010; Delgleize et al. 2016; Díez-Domingo et al. 2011; Earnshaw et al. 2012; Gouveia et al. 2017; Klok et al. 2013; Knerer, Ismaila, and Pearce 2012; Kuhlmann and Schulenburg 2017; Newall et al. 2011, 2016; O'Brien et al. 2009; Robberstad et al. 2011; Rozenbaum et al. 2010; Rubin et al. 2010; Strutton et al. 2012; Talbird et al. 2010; Hoek et al. 2012; Zhou et al. 2014). Our results are quantitatively similar to the body of cost-effectiveness literature of PCV. Most show that introducing PCV into national immunization programs is cost-effective when compared to no vaccination. However, our study improves on prior studies in several important ways.

We included more granular data than have previously been incorporated into a cost-effectiveness analysis of PCV. Because they are in essence predictive models, cost-effectiveness analyses are particularly sensitive to the accuracy of the modelling assumptions (Gray et al. 2011). Most of the prior studies did not collect detailed data on vaccine uptake, serotype coverage, incidence of disease in the population, disease sequelae, or direct and indirect costs (Vooren et al. 2014; Wu et al. 2015). Efficacies were based on the results of randomized controlled trials, but the existence and magnitude of herd-effect and serotype-replacement were usually based on assumptions and expert opinion (Vooren et al. 2014; Wu et al. 2015). Utilities were invariably based on studies conducted in other populations and time-periods (Herdman et al. 2016). Contrast this with our study, in which all inputs were directly measured in the population.

Costs associated with the administration of the vaccine were directly obtained from the Directorate of Health and not based on assumptions or list pricing. The direct costs associated with the outcome were sampled from individual-level otitis media visits, and hospital admissions for pneumonia and IPD. The distribution was empirically estimated through resampling of the observed costs, again allowing us to avoid assuming arbitrary uncertainty distributions. Days of work lost due to hospitalized pneumonia and IPD were modeled as a function of the individually observed hospital lengths of stay and the distribution was estimated through direct resampling. All cost and

outcome data were included in an overall Bayesian model, which propagated the uncertainty of each of the model parameters and produced a posterior distribution of the cost-effectiveness that includes an empirical probabilistic sensitivity analysis.

In general, a sensitivity analysis is necessary to explore the cost-effectiveness outcomes over a range of plausible input parameters, due to the subjective nature of underlying assumptions. Consensus statements from the World Health Organization and the International Society for Pharmacoeconomics and Outcome Research (ISPOR) require, at minimum, a one-way sensitivity analysis of each of the modelling assumptions (Mauskopf et al. 2018; Walker, Hutubessy, and Beutels 2010). Despite the considerable uncertainty associated with utilities, they were often not examined with sensitivity analyses (Blank and Szucs 2012; Chuck et al. 2010; Earnshaw et al. 2012; Gouveia et al. 2017; Klok et al. 2013; Newall et al. 2016; Strutton et al. 2012; Talbird et al. 2010). Similarly, cost inputs that were often purely assumed, based on expert opinion, or based on national tariffs given without any reference, were in many studies not included in a sensitivity analysis (Chuck et al. 2010; Earnshaw et al. 2012; Gouveia et al. 2017; Klok et al. 2013; Newall et al. 2016; Strutton et al. 2012; Talbird et al. 2010).

Our study is inherently different than most previous studies, in that it examines the cost-effectiveness of an intervention that has already been introduced. The most obvious strength of a post-implementation ecological design, is that it absolves the need to rely on untestable assumptions regarding herd-effect and serotype-replacement, which are instead directly observed. To our knowledge, only two previous studies have reported the post-implementation cost-effectiveness of PCV (Newall et al. 2016; Ray et al. 2009). Neither study directly estimated the impact of PCV on AOM, pneumonia or IPD but instead relied on previously published estimates or efficacy data (Newall et al. 2016; Ray et al. 2009).

## Conclusions

In this time series analysis of population-based data, we demonstrated a substantial direct impact on AOM in vaccinated children and provided the first published evidence of herd protection against AOM among older unvaccinated children. We showed a large decrease in pneumonia hospitalizations among both vaccinated and unvaccinated members of the population and confirmed previous papers showing an indirect impact. Our

results demonstrate that initially expensive vaccine interventions can be shown to produce such a decrease in health care consumption, that the resulting cost-savings offset the initial cost – all the while resulting in reduced suffering in the population. Our study highlights the importance of careful post-implementation studies; both as a tool to validate and calibrate the predictions made by pre-implementation cost-effectiveness studies, which rely heavily on unverifiable assumptions, and to provide evidence of vaccine benefit for policy makers.

## **Supplementary files**

### **Methods in detail**

Four independent models that described the secular trend of pneumococcal infections were fitted. The simplest model was an interrupted time series (ITS) model without an offset term. Calender-month effects were accounted for using dummy variables. The ITS model used the pre-vaccine period to estimate the trend. It predicted the monthly number of cases of the disease category, assuming the pre-vaccine trend would have continued if the vaccination had not occurred. A second ITS model was estimated, which included an offset term of all non-respiratory visits. This model used the pre-vaccine period to estimate the relationship between the outcome of interest and all non-respiratory visits. It also predicted the occurrence of disease in the post-vaccine period by incorporating the observed number of non-respiratory visits, and assumed the relationship between the disease category and non-respiratory visits would not have changed, had the vaccination not occurred. The third model included synthetic controls as covariates and used Bayesian variable selection to choose which of them to include (Bruhn et al. 2017). The prior for each synthetic control was set as a Dirac spike with a point-mass at zero (Dvorzak and Wagner 2019). The pre-vaccine period was used to estimate the relationship between the synthetic controls and the outcome of interest, and to select the optimal controls. This relationship was used to predict the trend in the post-vaccine period, had the vaccination not occurred. Finally, a two-step model was fitted, using a seasonal and trend decomposition (STL) and principal component analysis (PCA) (Shioda et al. 2018). STL was used to extract a smoothed trend for each of the synthetic controls. PCA was then used to extract the first principal component, which was used as a covariate in the final prediction model. Using data from the pre-vaccine period, leave-one-out cross-validation (LOOCV) was used to calibrate the models and calculate the average point-

wise likelihood for each model, diagnostic category and age-group. The average point-wise likelihoods were used as weights in a Bayesian model-stacking procedure, to produce the final stacked model used in the analysis.

## Supplementary figures

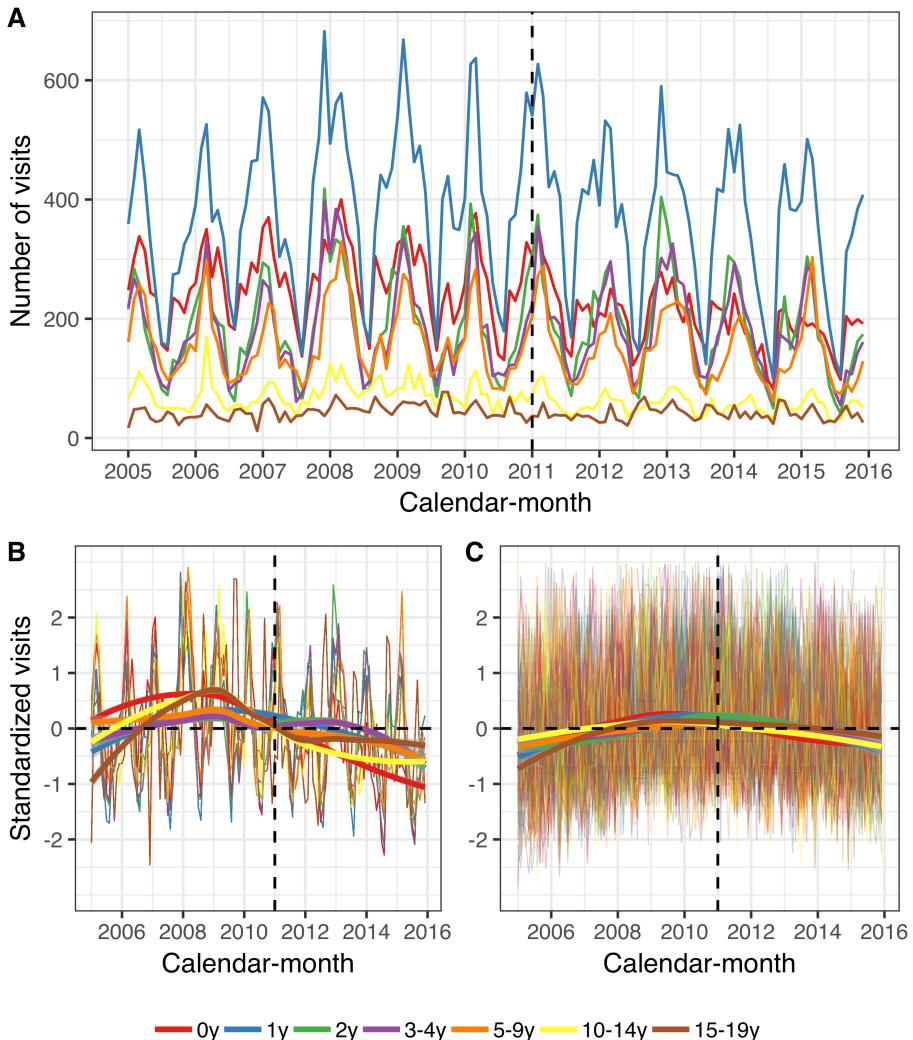


Figure 7 The figure presents the number of primary care visits among children younger than 20 years of age per calendar-month from 1 January 2005 to 31 December 2015. Children are divided into seven age-groups, listed in the figure legend. Panel A shows the monthly number of visits due to acute otitis media and its complications (AOM). Panels B and C, depict the standardized monthly number of AOM visits (Panel B) and all other visits (Panel C) per age-group. The Y-axis

represents the number of standard deviations the observed visits are from the mean of the entire period for each diagnosis and age-group. The horizontal dotted lines represent values that are zero standard deviations from the mean and the vertical dotted lines represent the beginning of the vaccine intervention. Locally estimated scatter-plot smoothing (LOESS) is used to produce an average trend. Panels B and C suggest that the number of both AOM visits and all other visits have decreased in the post-vaccine period, and that AOM visits have decreased to a larger degree.

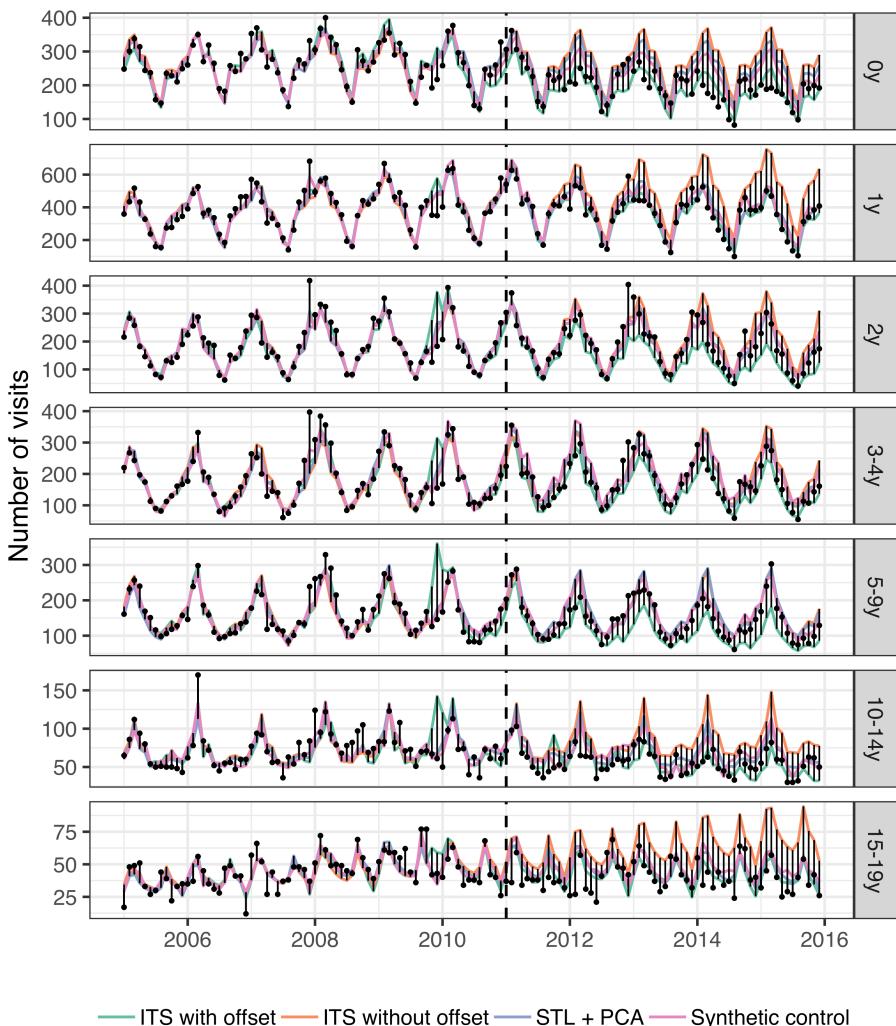


Figure 8 The observed and predicted number of visits for acute otitis media and its complications (AOM) from 1 January 2005 to 31 December 2015 for each age-group. Observed visits are illustrated as black points and the predicted number of visits are drawn as lines for each of the component models. The start of the vaccine period is delineated with a vertical black dotted line. Each component model was fitted to the

observed visits in the pre-vaccine period, and then used to predict the number of visits in the post-vaccine period, had the vaccine not been introduced. The distance between the observed and predicted visits for each calendar-month is depicted with a thin black line. Longer distances suggest a larger discrepancy. Note that the scale of the Y-axis differ between age-groups.

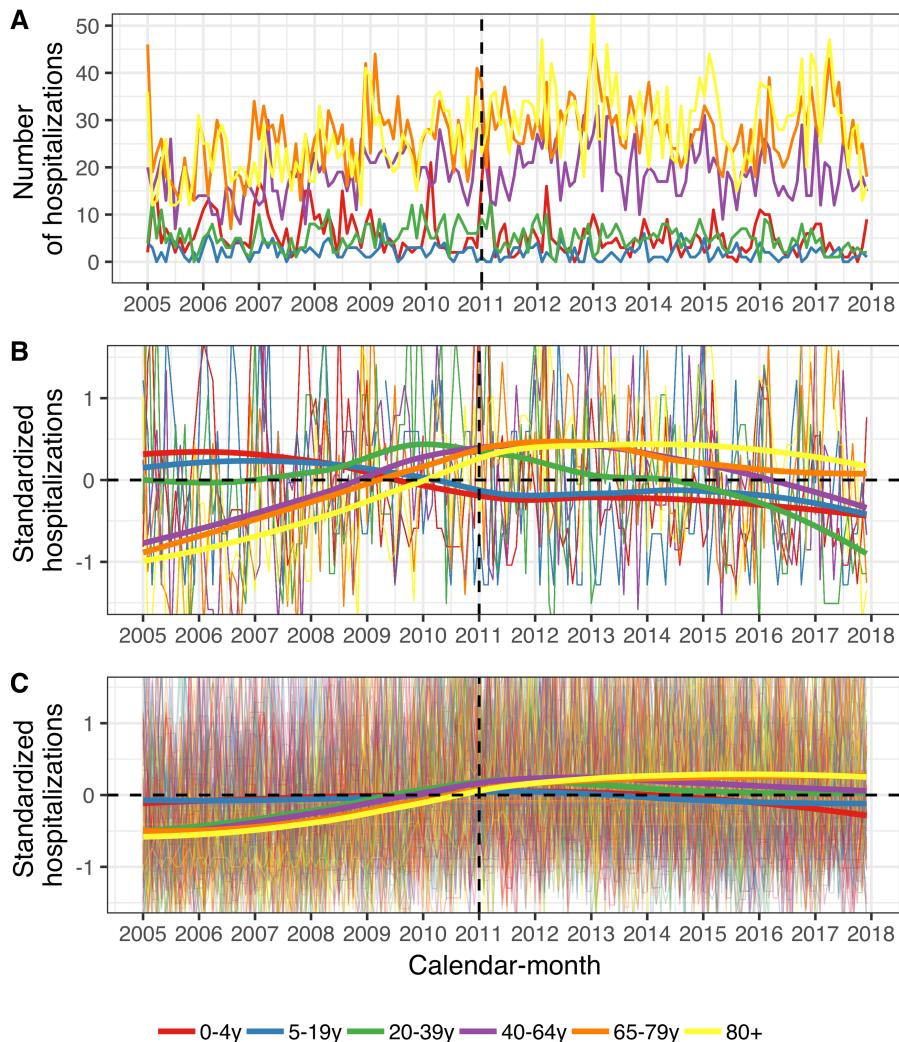


Figure 9 The figure presents the monthly number of hospital admissions for pneumonia and hospitalizations regardless of diagnosis from 1 January 2005 to 31 December 2017. Panel A shows the monthly number of pneumonia hospitalizations. Panels B and C depict the standardized monthly number of pneumonia hospitalizations (Panel B) and all other hospitalizations (Panel C) per age-group. The Y-axis shows how many standard deviations from the mean the observed hospitalizations are by diagnosis and age-group. The horizontal dotted lines represents values that are zero standard deviations from the mean and the vertical

dotted lines represent the start of the vaccine intervention. Locally estimated scatterplot smoothing (LOESS) is used to produce an average trend.

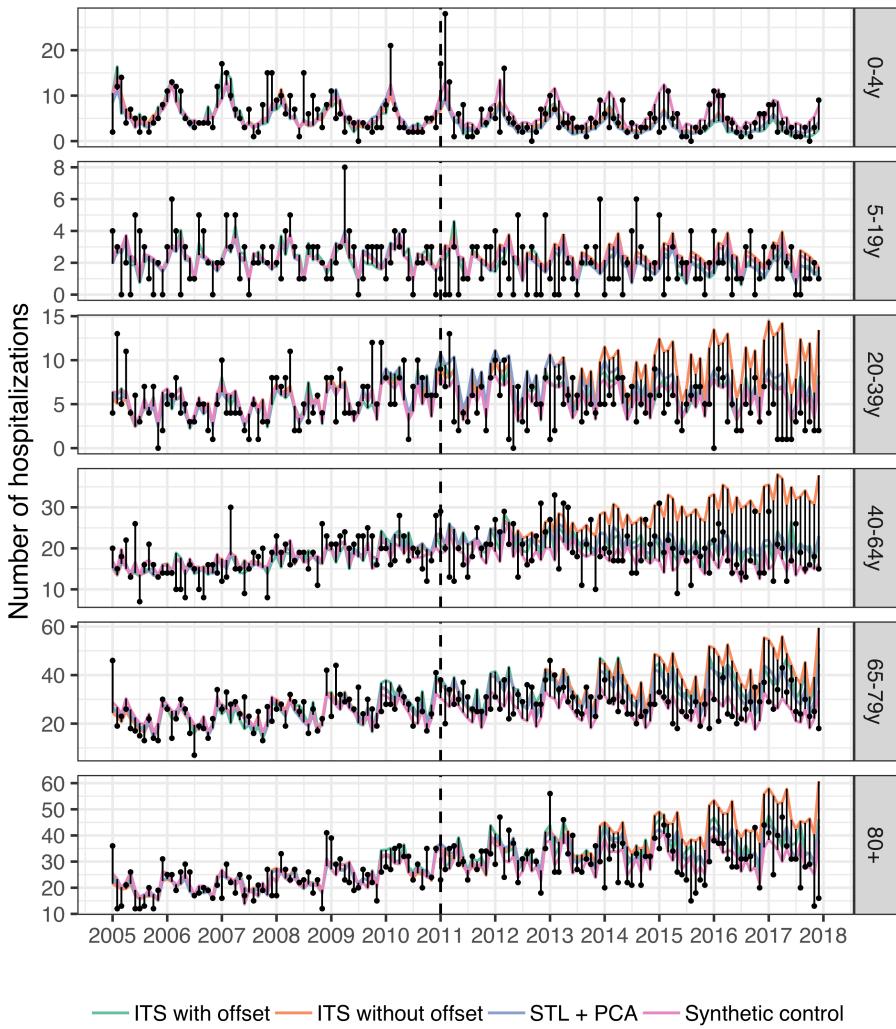


Figure 10 The observed and predicted number of pneumonia hospitalizations from 1 January 2005 to 31 December 2017 for each age-group. Observed cases are illustrated as black points and the predicted number of cases are drawn as lines for each of the component models. The start of the vaccine period is delineated with a vertical black dotted line. Each component model was fitted to the observed number of cases in the pre-vaccine period. They were then used to predict the number of cases that would have occurred in the post-vaccine period, had the vaccine not been introduced. The distance between the observed and predicted cases for each calendar-month is depicted with a thin black line. Longer distances suggest a larger discrepancy between observed and predicted cases. Note that the scale of the Y-axis differ between age-groups.

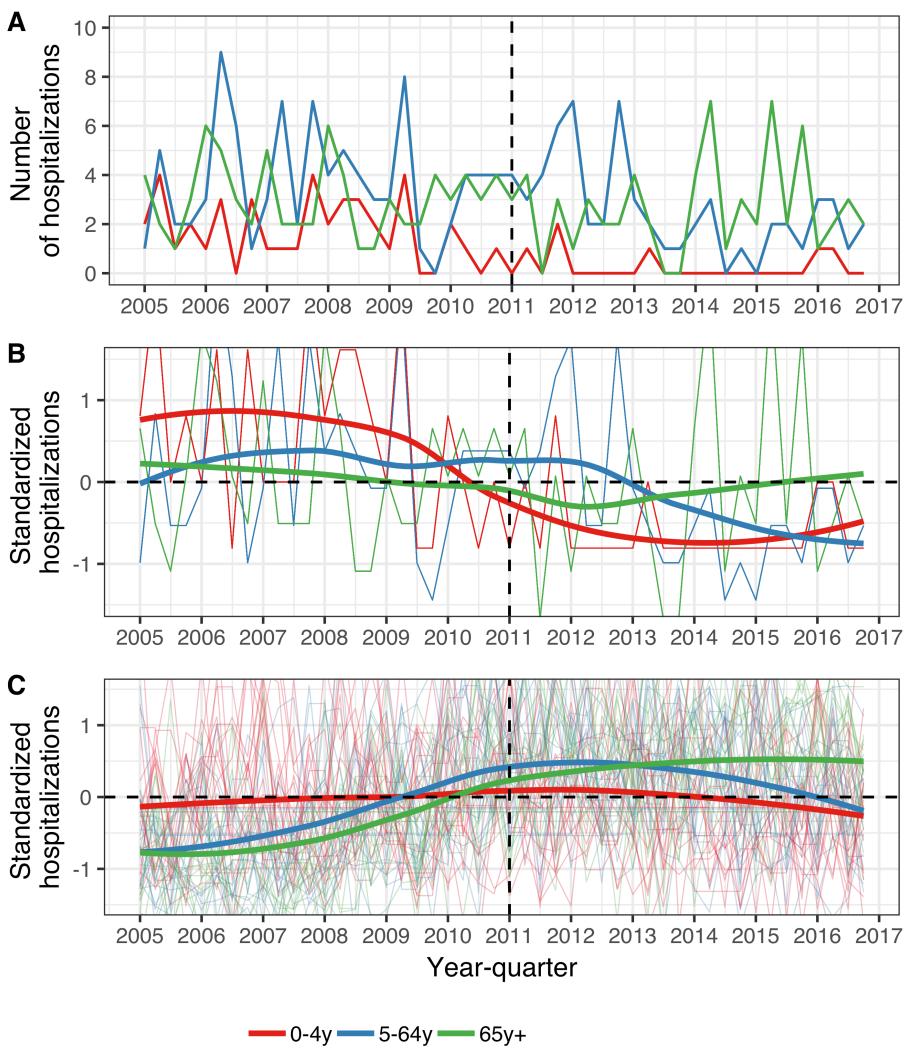


Figure 11 The figure presents the number of hospitalizations per year-quarter from 1 January 2005 to 31 December 2016. The population is divided into three age-groups, listed in the figure legend. Panel A shows the absolute quarterly number of hospital admissions due to invasive pneumococcal disease (IPD) regardless of serotype. Panels B and C, depict the standardized quarterly number of IPD hospitalizations (Panel B) and all-cause hospitalizations (Panel C) per age-group. The Y-axis represents the number of standard deviations from the mean hospitalizations for each quarter and each age-group. The horizontal dotted lines represent values that are zero standard deviations from the mean and the vertical dotted lines represent the start of the vaccine intervention. Locally estimated scatter-plot smoothing (LOESS) is used to produce an average trend. Panels B and C have been magnified to emphasize the interpretation of the trend line. Panels B and C show that standardized hospitalizations for IPD decreased in all age-groups, relative to the standardized hospitalizations regardless of cause.

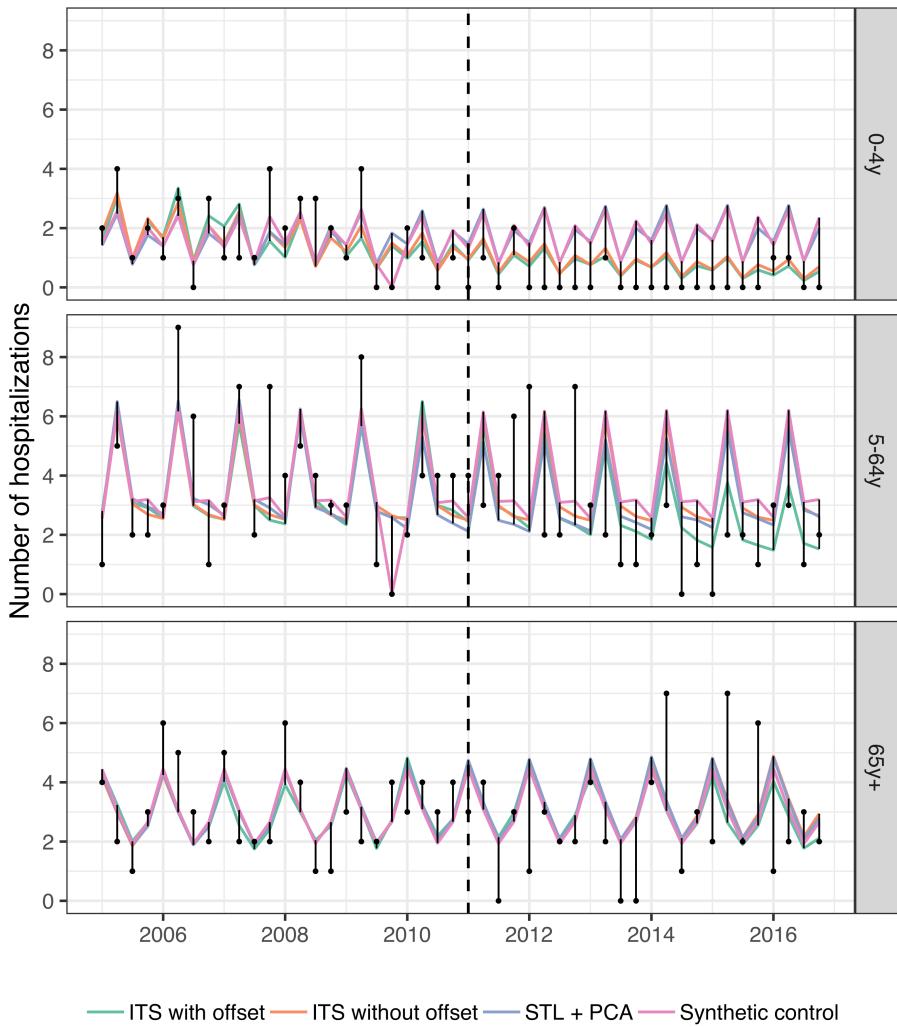


Figure 12 The observed and predicted number of IPD hospitalizations from 1 January 2005 to 31 December 2016 for each age-group. Observed cases are illustrated as black points and the predicted number of cases are drawn as lines for each of the component models. The start of the vaccine period is delineated with a vertical black dotted line. Each component model was fitted to the observed number of cases in the pre-vaccine period. They were then used to predict the number of cases that would have occurred in the post-vaccine period, had the vaccine not been introduced. The distance between the observed and predicted cases for each year-quarter is depicted with a thin black line. Longer distances suggest a larger discrepancy between observed and predicted cases.

## Supplementary tables

Table 6 The weights used to produce the final stacked model from the component models are presented. The weights for each component model were obtained by minimizing the leave-one-out mean squared error.

Disease category	Age-group	Synthetic controls	ITS with offset	ITS without offset	STL + PCA
AOM visits	0y	0.221	0.000	0.121	0.659
AOM visits	1y	0.149	0.000	0.610	0.241
AOM visits	2y	0.000	0.000	0.479	0.521
AOM visits	3-4y	0.661	0.000	0.339	0.000
AOM visits	5-9y	0.726	0.000	0.274	0.000
AOM visits	10-14y	1.000	0.000	0.000	0.000
AOM visits	15-19y	0.018	0.000	0.078	0.904
Pneumonia hospitalizations	0-4y	0.912	0.001	0.087	0.000
Pneumonia hospitalizations	5-19y	1.000	0.000	0.000	0.000
Pneumonia hospitalizations	20-39y	0.246	0.124	0.000	0.629
Pneumonia hospitalizations	40-64y	0.241	0.000	0.000	0.759
Pneumonia hospitalizations	65-79y	0.000	0.934	0.066	0.000
Pneumonia hospitalizations	80+	0.000	0.472	0.528	0.000
IPD hospitalizations	0-4y	0.001	0.999	0.000	0.000
IPD hospitalizations	5-64y	1.000	0.000	0.000	0.000
IPD hospitalizations	65y+	1.000	0.000	0.000	0.000

## Sensitivity analyses

### AOM

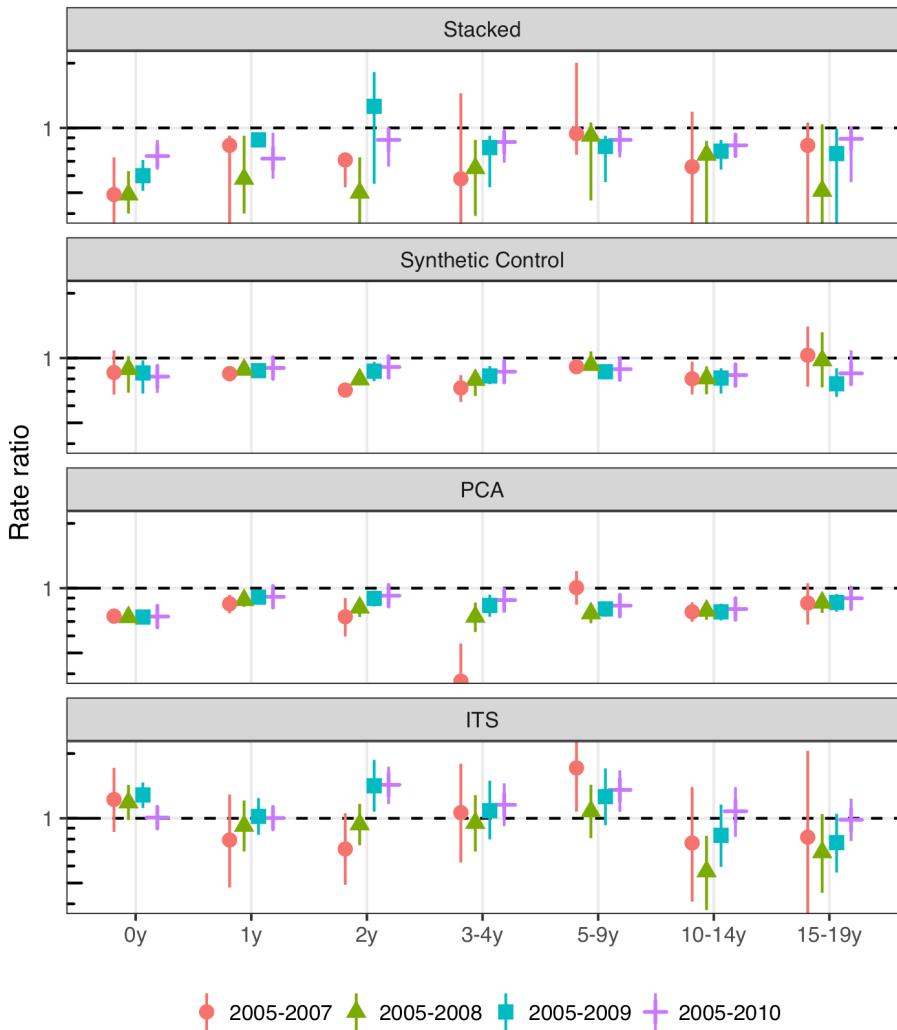


Figure 13 The figure illustrates the estimated rate ratio between the observed and predicted number of acute otitis media (AOM) visits in the post-vaccine period by model and the number of pre-vaccine years. Each age-group is shown separately on the X-axis. An additional pre-vaccine year is added from left to right, starting with the period 2005-2007 and ending with the full pre-vaccine period 2005-2010 that was used in the main analysis. The top frame shows the estimates for the final stacked model. The results are largely invariant to the number of pre-vaccine years, with a slight trend towards decreasing impact as more years are added.

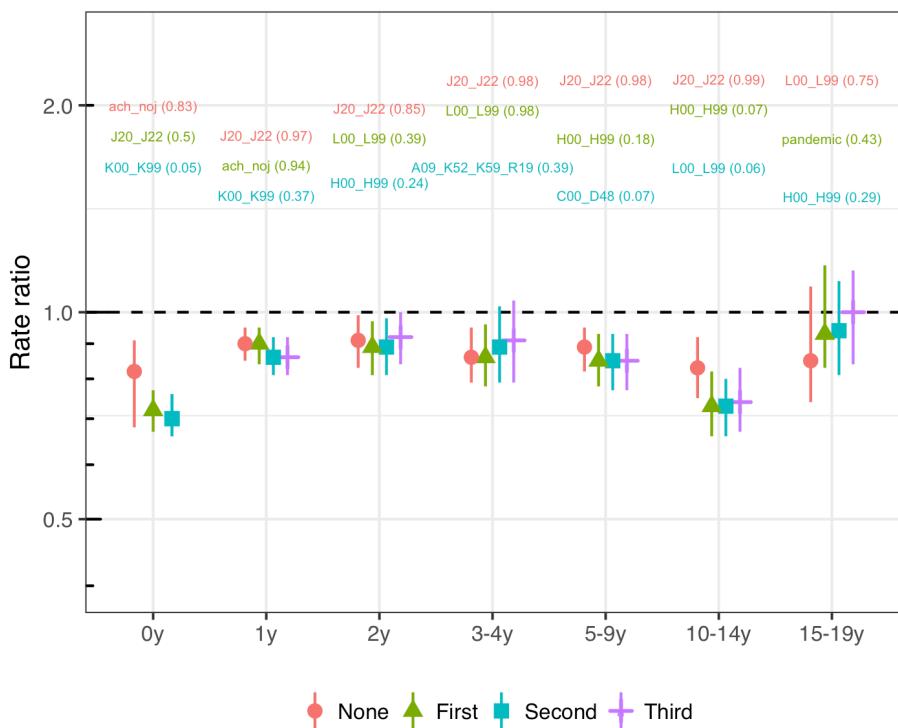


Figure 14 The figure depicts the estimated rate ratio between the observed and predicted number of acute otitis media (AOM) visits in the post-vaccine period for the synthetic control model. The leftmost point and confidence interval represents the full synthetic model used in the analysis, and the same colored label shows the top control and its associated inclusion probability in the Bayesian variable selection process. From left to right, the top control is removed, the model is refitted on the remaining controls and the corresponding rate ratio illustrated with a point and interval. The results are largely invariant to the controls used.

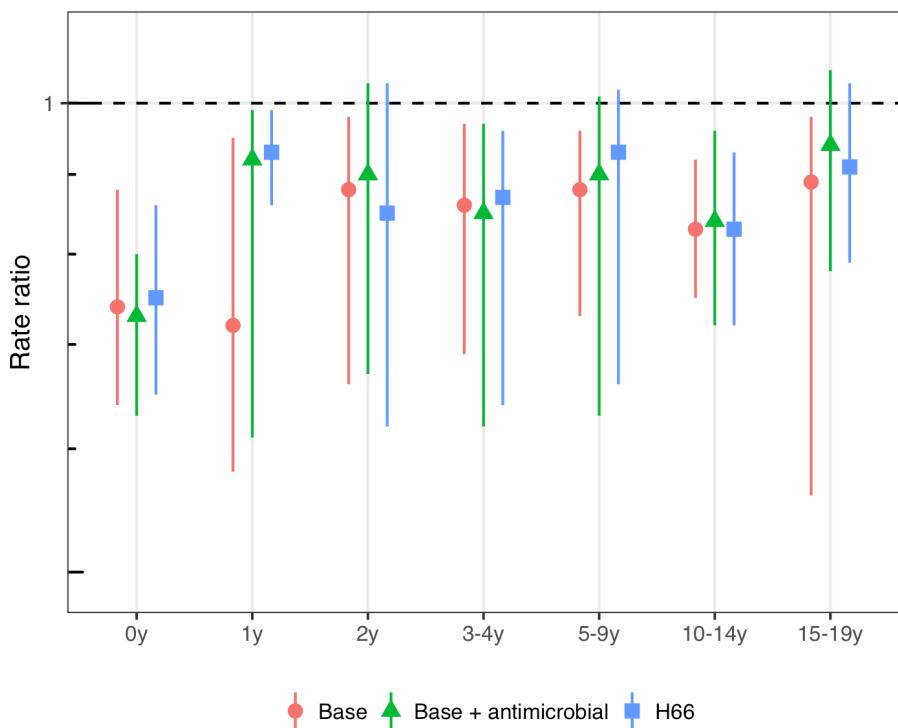


Figure 15 The figure illustrates the estimated rate ratio between the observed and predicted number of acute otitis media (AOM) visits in the post-vaccine period for the final stacked model using different case-definitions. The case-definition used in the main analysis is shown with a red point and intervals. The green point represents the same International Classification of Diseases, 10th revision (ICD-10) codes but only those resulting in an antimicrobial prescription. Finally the blue point represents only H66: Suppurative otitis media only. The results are largely invariant to the case-definition with the exception of one year old children.

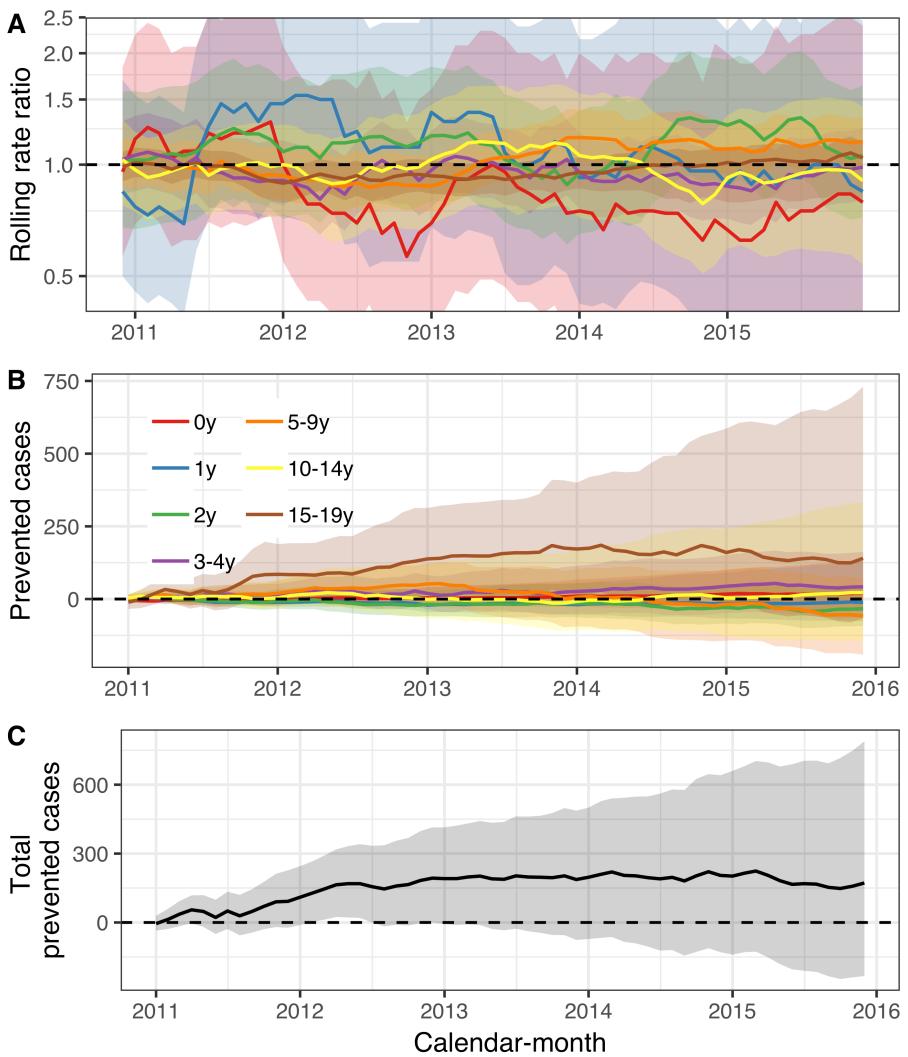


Figure 16 The population impact of the 10-valent *Haemophilus influenzae* protein D pneumococcal conjugate vaccine (PHiD-CV10) on outpatient visits for urinary tract infections (UTI) is summarized. In Panel A, the estimated 12-month rolling rate ratio between the observed and predicted number of UTI visits in the post-vaccine period (2011-2015) is shown per age-group. Panel B depicts the cumulative number of prevented UTI visits during the post-vaccine period (2011-2015) for each age-group along with 95% credible intervals. The total cumulative prevented UTI visits regardless of age-group is shown in Panel C. As expected, there was no discernible impact.

## Pneumonia

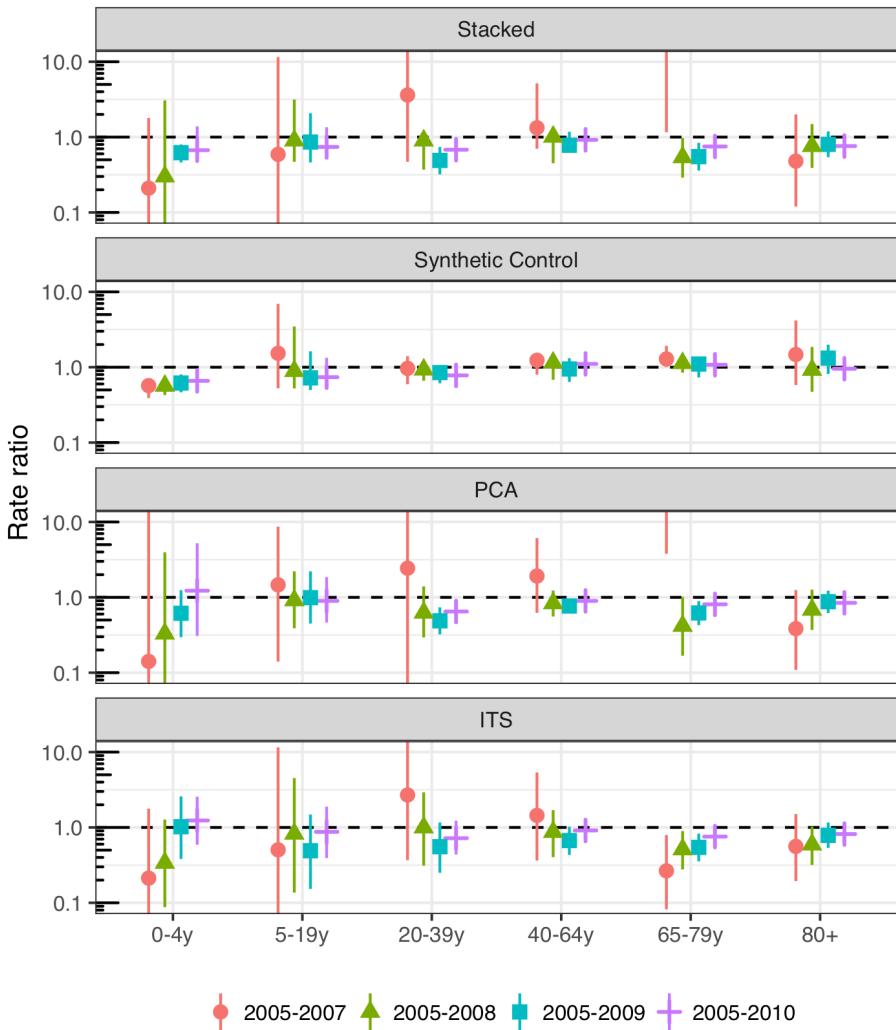


Figure 17 The figure illustrates the estimated rate ratio between the observed and predicted number of pneumonia hospitalizations in the post-vaccine period by model and the number of pre-vaccine years. Each age-group is shown separately on the X-axis. An additional pre-vaccine year is added from left to right, starting with the period 2005-2007 and ending with the full pre-vaccine period 2005-2010 that was used in the main analysis. The top frame shows the estimates for the final stacked model. The results are largely invariant to the number of pre-vaccine years. However, when only 2005-2007 are included, the estimates are severely unstable in the principal component analysis (PCA) model. The PCA model was given undue weight in the model stacking procedure, resulting in the same instability in the final stacked model. Despite this, the figure does not suggest that the inclusion of 2009 has large effects on the results. The 2009 influenza pan-demic does therefore not seem to unduly influence the results.

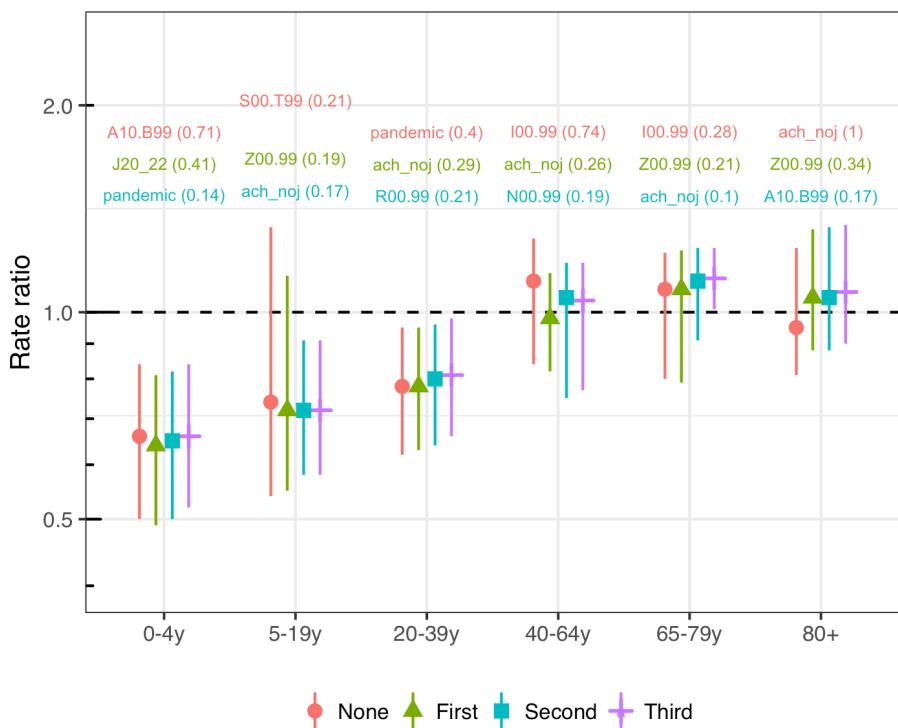


Figure 18 The figure depicts the estimated rate ratio between the observed and predicted number of pneumonia hospitalizations in the post-vaccine period for the synthetic control model. The leftmost point and confidence interval represents the full synthetic model used in the analysis, and the same colored label shows the top control and its associated inclusion probability in the Bayesian variable selection process. From left to right, the top control is removed, the model is refitted on the remaining controls and the corresponding rate ratio illustrated with a point and interval. The results are largely invariant to the controls used.

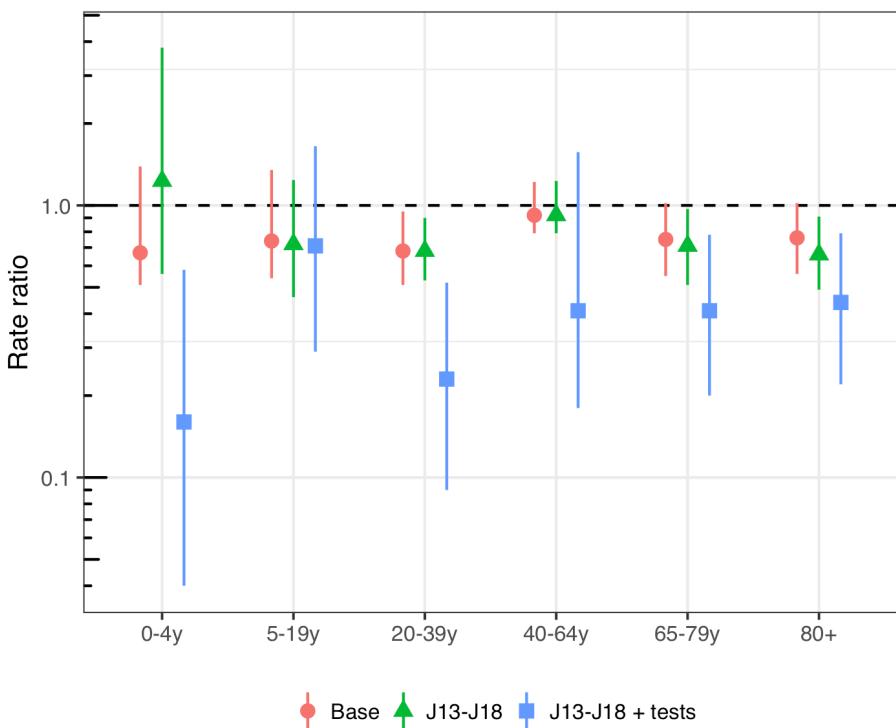


Figure 19 The figure illustrates the estimated rate ratio between the observed and predicted number of pneumonia hospitalizations in the post-vaccine period for the final stacked model using different case-definitions. The case-definition used in the main analysis is shown with a red point and intervals. The green point represents International Classification of Diseases, 10th revision (ICD-10) codes more specific for bacterial pneumonia. Finally the blue point represents the more specific ICD-10 definition of bacterial pneumonia, but only includes those hospitalizations in which radiographical and microbiological testing was performed. Using the most specific definition of pneumonia (blue), the impact of the 10-valent pneumococcal *Haemophilus influenzae Protein D* conjugate vaccine (PHiD-CV) is significantly larger in all age-groups.

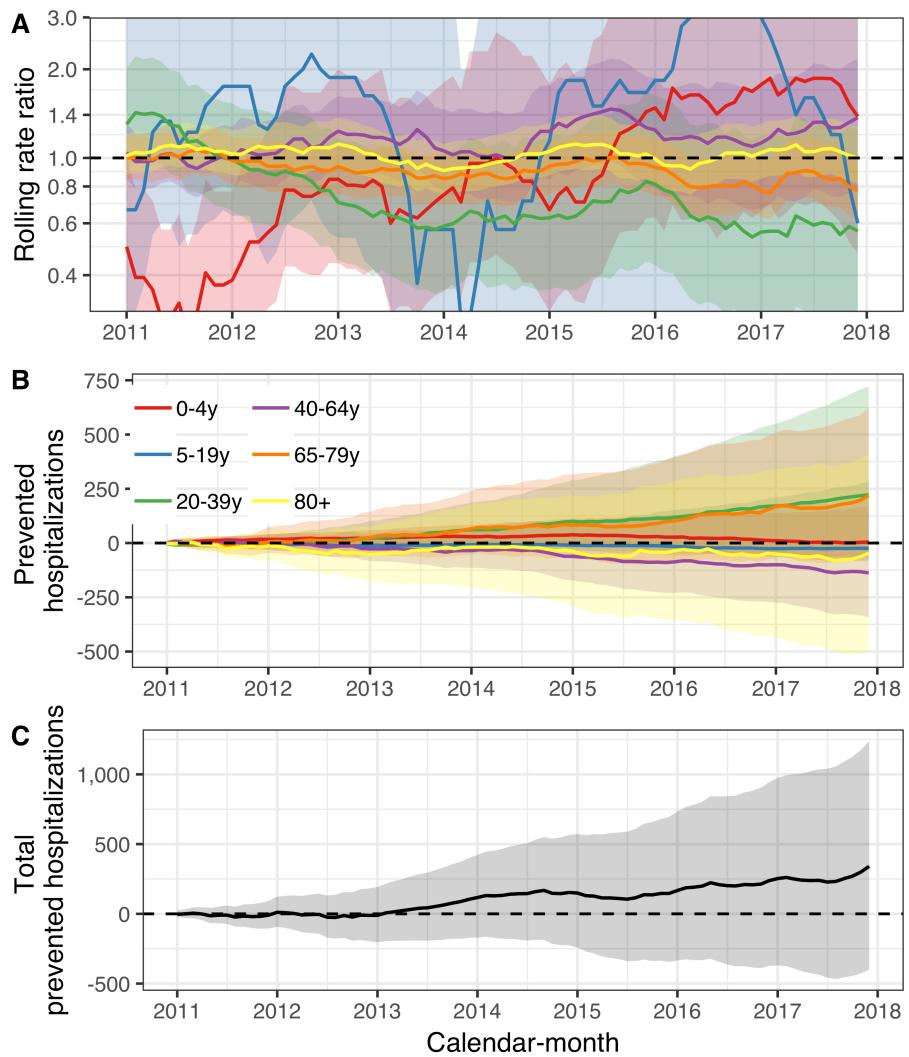


Figure 20 The population impact of the 10-valent *Haemophilus influenzae* protein D pneumococcal conjugate vaccine (PHiD-CV10) on outpatient visits for urinary tract infections (UTI) is summarized. In Panel A, the estimated 12-month rolling rate ratio between the observed and predicted number of UTI visits in the post-vaccine period (2011-2015) is shown per age-group. Panel B depicts the cumulative number of prevented UTI visits during the post-vaccine period (2011-2015) for each age-group along with 95% credible intervals. The total cumulative prevented UTI visits regardless of age-group is shown in Panel C. As expected, there was no discernible impact.

IPD

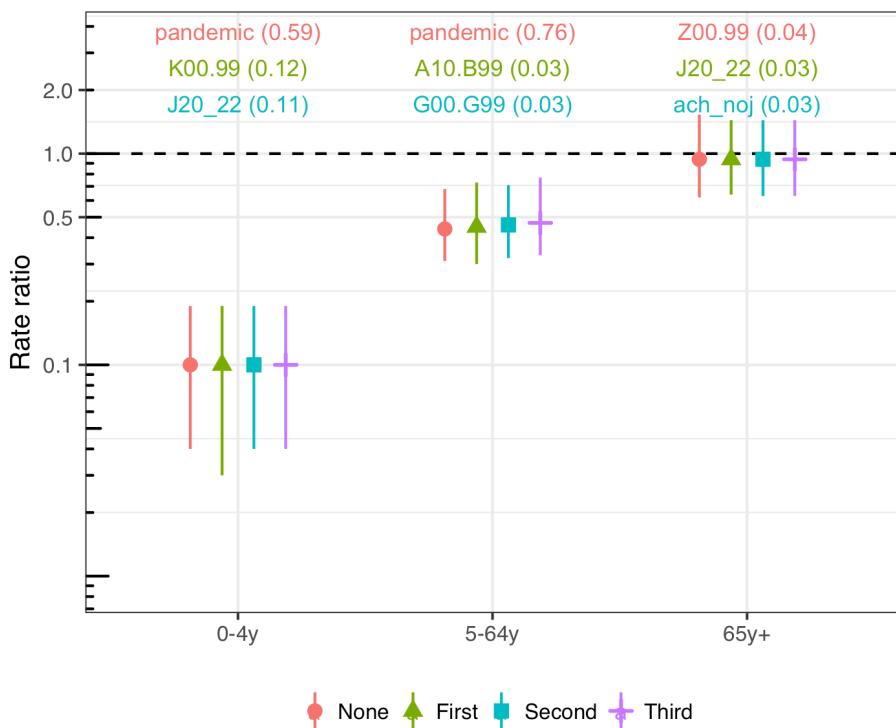


Figure 21 The figure depicts the estimated rate ratio between the observed and predicted number of hospitalizations for invasive pneumococcal disease in the post-vaccine period for the synthetic control model. The leftmost point and confidence interval represents the full synthetic model used in the analysis, and the same colored label shows the top control and its associated inclusion probability in the Bayesian variable selection process. From left to right, the top control is removed, the model is refitted on the remaining controls and the corresponding rate ratio illustrated with a point and interval. The results are largely invariant to the controls used.

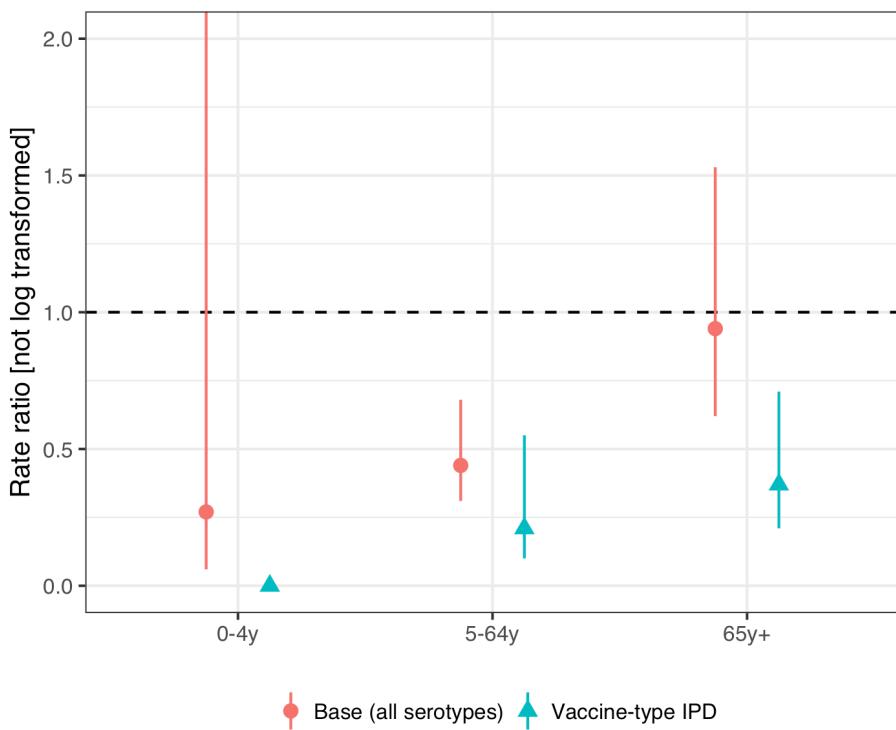


Figure 22 The figure illustrates the estimated rate ratio between the observed and predicted number of hospitalizations for invasive pneumococcal disease (IPD) in the post-vaccine period for the final stacked model using different case-definitions. Culture or PCR confirmed IPD regardless of serotype, the case-definition used in the main analysis, is shown with a red point and intervals. The green point represents vaccine-type IPD. The number of nonvaccine-type IPD in the pre-vaccine period was not large enough to fit any of the time series models. The figure shows that the impact of the 10-valent pneumococcal Haemophilus influenzae Protein D conjugate vaccine (PHiD-CV) on vaccine-type is large in all age-groups.

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