The population impact of the 10-valent pneumococcal conjugate vaccine on healthcare consumption and cost

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Thesis for the degree of Philosophiae Doctor

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May 2019

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

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Maí 2019

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Thesis for a doctoral degree at the University of Iceland. All right reserved. No part of this publication may be reproduced in any form without the prior permission of the copyright holder.

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ISBN (apply at <http://www.landsbokasafn.is/>)

Printing by Háskólaprent

Reykjavik, Iceland 2019

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 miðeyrnabólgum, sem ganga flestar yfir án inngrips, til blóðsýkinga og heilahimnubólga sem krefjast innlagnar á sjúkrahús. Þrátt fyrir að miðeyrnabólgur 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 náði ekki útbreiðslu fyrr en 1983, þegar 23-gilt fjölsykrubóluefni kom á markaðinn. Það gaf hins vegar ekki góða ónæmissvörun í börnum. Til þess þurfti próteintengingu. Sjö-gilt samtengt pneumókokka bóluefni kom á markaðinn árið 2000. Fjöldi rannsókna hafa sýnt fram á vernd þess gegn miðeyrnabólgum, rörísetningum, lungnabólgum og ífarandi sýkingum hjá börnum. Einnig hefur verið sýnt fram á hjarðónæmi hjá fullorðnum. Samtengd bóluefni gegn 10 og 13 sermigerðum pneumókokka voru framleidd í kjölfarið. Í apríl 2011 var 10-gilda samtengda pneumókokka bóluefnið innleitt í ungbarnabólusetningar á Íslandi.

Markmið þessarar 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 bólusetningarinnar voru 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 sjúkraskrá Landspítala Háskólasjúkrahús fyrir tímabilið 1. Janúar 2005 – 31. Desember 2017. Öllum pneumókokkabólusetningum og sýklalyfjaávísunum var safnað úr bólusetningargagnagrunni og lyfjagagnagrunni Embætti Landlæknis. Allar læknisheimsóknir vegna öndunarfærasýkinga voru dregnar úr samskiptaskrá heilsugæslustöðva og sjúkraskrá Landspítala Háskólasjúkrahús, 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 fæðingarárgöngum 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 miðeyrnabólgur, 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 reyndust vera 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 öndunarfærasýkinga. 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 hjarðnæmi 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 fyrir miðeyrnabólgu, lungnabólgu og ífarandi sýkingar. Að teknu tilliti til sparnaðar vegna færri sýkinga, sparaði bóluefnið X milljarða íslenskra króna á fyrstu sjö árum eftir innleiðingu þess.

Rannsóknirnar sem byggja þessa ritgerð 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 var heildarkostnaður innleiðingarnar enginn. Þvert á móti sparaði hún X milljarða.

**Lykilorð:** *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 among children, and tympanostomy tube placements are the most common surgical procedure 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 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 Landspitali 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 was 22% 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.

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 as 5.8% (95% CI 1.6%-9.8%). 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 X million Icelandic kronas in the first seven 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

Fanka ek mildan mann  
eða svá matar góðan  
at værit þiggja þegit  
eða síns féar  
svá gjöflan  
at leið sé laun ef þiggr (*Hávamál, 39*)

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 ow. 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.

I would also like to thank my co-advisors, Clinical Professor of Microbiology Helga Erlendsdóttir and Professor and Chief of Clinical Microbiology Dr. Karl G. Kristinsson, for their guidance and knowledge over the past five years. Every Tuesday, the study group met for an hour-long meeting in Karl’s office. Invariably present were Ásgeir, Helga and Karl. Each of the doctoral students were provided an opportunity to discuss their accomplishments over the past week, and seek assistance for issues that had come up. There; Ásgeir, Helga and Karl offered their collective wisdom regarding the hidden curriculum of scientific research, and advice and 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.

The last member of my doctoral committee, Professor of Statistics Dr. Birgir Hrafnkelsson, provided support and mentoring in the field of statistics. Birgir did not coddle me. He pushed me to do all my own statistical work and provided help if needed. As a result, I learned to programme in the R statistical language and gained an appreciation and understanding of clinical epidemiology and applied statistics – both of which I intend to pursue in the future. For this, I am grateful.

I would like to thank the other members of our research group, who often attended the Tuesday meetings and contributed to my education and research. These included Dr. Gunnsteinn Haraldsson and Dr. Martha Hjálmarsdóttir, who provided helpful guidance and advice, and the two other PhD students in the group; Sigríður Júlía Quirk and Dr. Samúel Sigurðsson. I would especially like to thank Samuel for our collaboration during the final two years of my studies. When I was plagued with writer’s block, he was able to draft an article within days. He taught me that writing is iterative, and that the first draft is exactly that – the first draft. Without this lesson, I am unsure whether I could have written this thesis.

The data upon which my thesis is built were collected from several registries. I would like to thank Guðrún Kr. Guðfinnsdóttir at the Icelandic Directorate of Health; Elísabet Guðmundsdóttir and Ingibjörg Richter at Landspitali University Hospital; Margrét Rósa Kristjánsdóttir at Icelandic Health Insurance and Margrét Valdimarsdóttir at Statistics Iceland, for their work extracting data from their respective registries. Most of the data coordination was overseen by Guðrún, and I thank her especially for her patience and the assistance she provided. With the exception of my doctoral committee, she is my most frequent email recipient, having accumulated 93 emails from me during the past two years alone.

During the course of my studies, I developed an interest in statistics and methodology. I completed several courses in probability and statistics and was introduced to Professor of Statistics Dr. Thor Aspelund and Dr. Sigrún Helga Lund. As time passed, we became friends, and I learned to trust their advice. I would like to thank both for the contributions to my training, and for the support they have shown me during my studies.

I would like to thank Associate Professor of Epidemiology at Yale School of Public Health Dr. Daniel Weinberger for his commitment to open science. We met at ISPPD in 2018 and spoke after a session he chaired. We discussed methodological aspects of pneumococcal epidemiology and he informed me of a novel time series method recently published by his group. He then informed me that all the statistical code had been provided online, open to all. I incorporated this code into my final paper. This experience has convinced me that open science is the way forward, and I vow to disseminate my data and code when possible for the benefit of all.

It takes a village to raise a doctoral student. I would not have been able to do this without the support of my family and friends. I thank Kristín, my wife and mother of my child (soon children), for her patience and understanding. A PhD is completed during evenings and weekends, and she has had to endure the sight of my face illuminated by the harsh blue light of a computer screen for far too long. Breki, my son, I thank for reminding me of the balance I must maintain between work and family. He expresses the appropriate amount of contempt for my computer, which robs him of his father for long stretches of time. I thank my brother, Daníel, for reminding me of what a obnoxious over-achiever I have become. My parents Andrea and Eythor Haraldsson, I thank for their excellent parenting skills, which in my humble opinion have produced some the greatest minds in academia. Their sincere interest in my niche research proves that parents’ love for their child knows no bounds.

I would especially like to thank my mother. In addition to literally being the reason I am here today, she has directly contributed to my training as a researcher. A graduate of Smith College with a major in English, she has read every single sentence I have written since the beginning of my PhD, and advised on punctuation, grammar, and the structure of paragraphs and sentences. Each manuscript I have written has been passed to her for multiple language editing revisions, and this 300 page monograph is no exception. She taught me how to write well. Thank you.