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

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Ágrip

*Streptococcus pneumoniae* er Gram-jákvæð tvíhnettla 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 vægar, þá eru þær algengasta orsök læknisheimsókna og sýklalyfjaávísanna barna. Rörísetningar í eyru eru algengustu aðgerðir sem krefjast svæfingar í börnum.

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 olli þó ekki góðri ónæmissvörun í börnum. Til þess þurfti próteintengingu. Sjö-gilt samtengt pneumókokka bóluefni kom á markaðinn árið 2000. Fjöldi rannsókna hafa sýnt fram á vernd 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%. Samanburður á tíðni ceftriaxone meðferðar við miðeyrnabólgu á Barnaspítala Hringsins fyrir og eftir upphaf bólusetningar var notaður til að áætla áhrif á bóluefnisins á alvarlegar miðeyrnabólgur, og reyndist vera 55% 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 skoðaði áhættu á sjúkrahúsinnlögn 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 occured 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

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eða svá matar góðan  
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The last member of my doctoral Professor of Statistics Dr. Birgir Hrafnkelsson

Often also present at these meetings were other members of the pneumococcal research group. These included

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