Pneumococcal Haemophilus Influenzae Protein D Conjugate Vaccine (PHiD-CV10) reduced Outpatient Antimicrobial Purchases in a Cluster Randomised Trial

A.A. Palmu1* MD, J. Jokinen2 PhD, H. Nieminen1 MD, H. Rinta-Kokko2 MSc, E. Ruokokoski2 MSc, T. Puumalainen3 MD, D. Borys3 MD, P. Lommel3 MSc, M. Traskine3 MSc, M. Moreira3 MD, L. Schuerman3 MD, T.M. Kilpi2 MD, Prof.

1Department of Vaccination and Immune Protection, National Institute for Health and Welfare, FinnMedi I, Biokatu 6, FI-33520 Tampere, Finland
2Department of Vaccination and Immune Protection, National Institute for Health and Welfare, P.O. Box 30, FI-00271 Helsinki, Finland,
3Global Vaccine Development, GlaxoSmithKline Vaccines, Parc de la Noire Epine, 20, Avenue Fleming, 1300 Wavre, Belgium
4Department of Infectious Diseases Surveillance and Control, National Institute for Health and Welfare, P.O. Box 30, FI-00271 Helsinki, Finland,
5GlaxoSmithKline Vaccines, Piispansilta 9A, FI-00231, Espoo, Finland (Current affiliation: Ministry for Social Affairs and Health, Meritullinkatu 8, FI-00023, Government, Helsinki, Finland)

*Corresponding author:
Arto A. Palmu, MD, PhD
National Institute for Health and Welfare (THL)
Finn-Medi I, Biokatu 6, 33520 Tampere, Finland
Tel. +358 29 524 7910, arto.palmu@thl.fi
Fax. +358 32532 390

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Background
Antimicrobials are frequently prescribed to children for respiratory tract infections including otitis, tonsillitis, sinusitis and pneumonia. We have evaluated the impact of the 10-valent PHiD-CV (GlaxoSmithKline Vaccines) on antimicrobial purchases.

Methods
In this nationwide phase III/IV cluster-randomised, double-blind trial, children <19 months received PHiD-CV10 in two thirds of clusters (N=52) or hepatitis B or A vaccine as control in 26 clusters according to 3+1 or 2+1 schedules (infants <7 months) or catch-up schedules (children 7-18 months of age). The main objective for the antimicrobial treatment outcome was to assess vaccine effectiveness (VE) against outpatient prescriptions of antimicrobials recommended by the national treatment guidelines for acute otitis media in Finland (amoxicillin with and without enzyme inhibitor, phenoxymethylpenicillin, cefuroxime, cefaclor, sulfadiazine and trimethoprim, clarithromycin, azithromycin) in children who received at least one dose of study vaccine before seven months of age. Blinded follow-up lasted from the date of first vaccination (from February 2009 through October 2010) to December 31, 2011. Outcome data i.e. all purchased antimicrobial prescriptions, were collected through the benefits register of the Social Insurance Institution of Finland. This and the nested acute otitis media trial are registered at ClinicalTrials.gov: NCT00861380;NCT00839254.

Results
Over 47000 children were enrolled. In 30527 infants <7 months of age at enrolment, 98436 outpatient antimicrobial purchases were reported with incidence of 1·69 per person-year in the control clusters. Analysis of the main objective included 91% of all antimicrobial purchases meaning 31982 purchases in the 26 control and 57964 purchases in the 52 PHiD-CV10 clusters. The VE was 8% (95% CI 1 to 14%) and the incidence rate difference 0·12 per person-year corresponding to the number needed to vaccinate (NNV) of 5 (95% CI 3 to 67) to prevent one purchase during the two-year follow-up for combined PHiD-CV10 3+1 and 2+1 infant schedules. The VEs were identical for the two infant schedules. In the catch-up schedules, the VE was 3% (95% CI: -4 to 10%).

Conclusions
We showed that the PHiD-CV10 vaccine reduced the considerable load of outpatient antimicrobial purchases in children. Despite low relative rate reductions the absolute rate reductions were substantial due to high incidence of the outcome. This would translate into >12000 fewer antimicrobial purchases per year in children under 24 months of age in Finland with a birth cohort of 60000 children.

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Registration: ClinicalTrials.gov, NCT00861380 and NCT00839254.

Author Keywords: vaccine, pneumococcus, clinical trial, antimicrobial use, infant
Panel: Research in context

Systematic review
We searched PubMed and Cochrane Library for reports published in English before July 4, 2013, with the following search terms in any fields: “efficacy” or “effectiveness” and “clinical trial” or “controlled” and “conjugate vaccine” and “antimicrob* OR antibiot*”. One randomised clinical trial with the seven-valent pneumococcal conjugate vaccine (PCV7) administered to infants was identified. Another randomised trial with nine-valent conjugate vaccine given to children 12 to 35 months of age in day care centres was identified. No randomised clinical trial data were published with the 2+1 infant schedule. One observational prospective cohort study was identified with PCV7 infant 2+1 schedule in infants. No clinical trial data were available for the ten or 13-valent PCVs.

Interpretation
Our study is the first double-blind, randomised controlled trial to document the effectiveness of the 10-valent pneumococcal conjugate vaccine against antimicrobial use and the first randomized trial to show the effectiveness of an infant 2+1 schedule. The vaccine effectiveness estimates of both 3+1 and 2+1 schedules in the current trial are low, yet slightly higher compared to that reported for the 3+1 schedule of the seven-valent pneumococcal conjugate vaccine. The low relative vaccine effectiveness estimates translate into considerable absolute public health impact due to the high incidence of antimicrobial use in children.
INTRODUCTION

Antimicrobials are frequently prescribed to treat mucosal respiratory infections in children. High incidence of respiratory infections coupled with difficult clinical and aetiological diagnosis, especially in determining whether bacterial or viral, as well as parental expectations for active treatment have led to significant overuse of antimicrobials. Although encouraging decreasing trends have been recently reported,1,2 the overuse of antimicrobials remains a public health challenge. While most of the mucosal respiratory infections are viral, *Streptococcus pneumoniae* and *Haemophilus influenzae* are major pathogens in acute otitis media (AOM) in children,3-5 and AOM is the most common indication for antimicrobial treatment in children in high income countries.2,6,7

In clinical trials, pneumococcal conjugate vaccines (PCV) have been shown to reduce vaccine serotype-specific AOM by roughly 60%.5,8,9 However, the impact on overall AOM has been considerably lower, varying from 0 to 34%, due to a variety of pathogens causing the disease and also due to replacement disease by pneumococcal non-vaccine serotypes and by other pathogens. In observational studies reductions of 19% on average have been observed in otitis media diagnoses after the implementation of national vaccination programmes using the first-licensed seven-valent PCV (PCV7; Prevenar/Prevnar™, Pfizer, Philadelphia, PA, USA).10

We have earlier reported the effectiveness of the ten-valent pneumococcal conjugate vaccine PHiD-CV10 (Synflorix™, GlaxoSmithKline Vaccines, Rixensart, Belgium) against invasive pneumococcal disease in a cluster randomised clinical trial setting.11 We have now evaluated its impact on outpatient antimicrobial purchases.
METHODS

Trial design and participants
The Finnish Invasive Pneumococcal disease (FinIP) vaccine trial was designed as a phase III/IV double-blind cluster-randomised, controlled field trial. The detailed trial design has been presented earlier.11

Trial enrolment and vaccinations were performed in collaborating Finnish health care centres (HCC) and their local well-baby clinics (WBC, N=651) by the nurses (N>2200) who are responsible for routine health follow-up and immunisations of children. A parallel immunogenicity, carriage, and AOM trial conducted by the Tampere University Vaccine Research Centre (TAUVRC) used the same cluster-randomised design contributing to the results.12 TAUVRC enrolled subjects at 15 dedicated study clinics.

The enrolment started in February 2009 and ended in fall 2010 when PCV was introduced in the Finnish National Vaccination Programme for children born on June 1, 2010 or later. A child was eligible for enrolment if he/she was six weeks to 18 months of age, had not received and was not anticipated to receive any of the study vaccines during the study follow-up, nor had any study vaccine-specific or general contraindications to immunisations.

Cluster randomisation and masking
The areas of the participating HCCs were divided geographically into 72 clusters using administrative boundaries (WBC/HCC/municipality) and the birth cohort size. Municipalities (N=11) covered exclusively by TAUVRC were split into six additional clusters. The treatment was allocated to the 78 clusters using two infant schedules (3+1 or 2+1) and a randomisation ratio of 2:2:1:1 (PHiD-CV10-3+1:PHiD-CV10-2+1:Control-3+1:Control-2+1). Treatment allocation was stratified according to the size of the birth cohort (below/above average), TAUVRC trial enrolment (50 of 78 clusters), and urbanity (24 urban and 54 rural clusters). In each cluster and each WBC, all enrolled children received the same blinded study vaccine; either PHiD-CV10 or control. The details of the randomisation and masking were described earlier.11

Procedures
The pneumococcal study vaccine included 1 µg of each capsular polysaccharide (PS) for serotypes 1, 5, 6B, 7F, 9V, 14 and 23F, and 3 µg for serotype 4 each individually conjugated to protein D of nontypeable Haemophilus influenzae, and 3 µg of capsular polysaccharide of serotypes 18C and 19F conjugated to tetanus and diphtheria toxoids, respectively.
Hepatitis B virus (HBV) vaccine (Engerix B™ 10 µg/0·5 ml) was used as a control vaccine for children enrolled before 12 months of age and hepatitis A virus (HAV) vaccine (Havrix™ 720 Junior) for children enrolled at or after the age of 12 months. The study vaccines were manufactured by GlaxoSmithKline Vaccines.

The infant cohort included children enrolled under seven months of age who received either three (minimum 4-week intervals) or two (minimum 8-week interval) primary vaccine doses and a subsequent booster dose at least four months after the last primary dose, but not earlier than 11 months of age (infant 3+1 and 2+1 cohorts, respectively). Children enrolled from 7 through 11 months of age were administered two doses at least four weeks apart followed by a booster dose at least four months after the second primary dose (catch-up cohort 7 to 11 months at enrolment). Children enrolled from 12 through 18 months of age received two doses at least 6 months apart (catch-up cohort 12 to 18 months at enrolment). The study vaccinations were mostly given concomitantly with the vaccines of the national vaccination programme.
Data on the outpatient antimicrobial purchases were collected through the administrative benefits register of the Social Insurance Institution of Finland. All permanent residents in Finland are covered by the Finnish National Health Insurance and are eligible for reimbursements for costs of reimbursable prescribed medicines, including all antimicrobials for treatment or prevention of infections. Pharmacies submit the reimbursement claims of purchased prescriptions for medicines automatically online to the Social Insurance Institution of Finland. Antimicrobial drugs are not available in Finland without a physician’s prescription. The register data include the ATC code and generic name of the drug, the quantity in absolute terms and defined daily doses (DDD), pharmaceutical form and concentration, date and costs of the drug purchased, and the identification of the subject using the Finnish personal identity code. The actual indication for which the antimicrobial was prescribed is not systematically recorded in the register. However, in part of the prescriptions the indication could be extracted from the physician’s free text for prescription including dosing and other instructions intended for the patient. Data on hospital antimicrobial consumption are not available in this register, and were thus not considered. In 2009 to 2012, 12% of all systemic antimicrobials were sold to hospitals and 88% for outpatient use through pharmacies (www.fimea.fi).

Our main objective was to assess the vaccine effectiveness (VE) against outpatient purchases of antimicrobials recommended for treatment of AOM in the national guideline in Finland. Here, these are defined as antimicrobials recommended for AOM and include amoxicillin without (ATC-code J01CA04) and with enzyme inhibitor clavulanic acid (J01CR02), phenoxymethylpenicillin (J01CE02), cefuroxime (J01DC02), cefaclor (J01DC04), sulfadiazone and trimethoprim (J01EE02), clarithromycin (J01FA09), and azithromycin (J01FA10).

Safety follow-up has been reported elsewhere.

**Statistical analysis**

The primary objective for the antimicrobial treatment outcome was to assess VE against outpatient purchases of antimicrobials recommended for AOM in children who received at least one dose of PHiD-CV10 before seven months of age either in 3+1 or 2+1 schedule. The sample size for the trial was based on the primary objective of the trial, i.e. VE against the invasive pneumococcal disease.

For statistical analyses overall and ATC-code-specific antimicrobial purchases including all (or ATC-code-specific) purchases on a given day and the successive day were combined and regarded as one purchase. Intention-to-treat (ITT) follow-up for each subject started at the date of the first vaccination and ended on December 31, 2011. Incidences were calculated as arithmetic mean of cluster-specific incidences and also as number of cases divided by the follow-up in PHiD-CV10 and Control groups for the main results. To account for between-cluster variability in the incidence of antimicrobial prescriptions, negative binomial model was used for the analysis of the effectiveness. Frequencies of antimicrobial prescriptions were grouped by cluster and the cluster-specific person-years were used as weights in the analysis. When estimating the effectiveness by schedule, treatment variable was used in the model as three-level factor (PHiD-CV10-3+1; PHiD-CV10-2+1; control). Factors used for stratified randomisation were included in the model as explanatory variables. Profile likelihood method was used to estimate the 95% CIs for the treatment parameter. VE was calculated as 1 minus rate ratio.

Incidence rate difference was calculated as the difference of incidence rate estimates in the PHiD-CV10 and control groups using negative binomial model. Confidence interval (CI) was calculated using the delta method.

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To investigate the effectiveness on recurrent antimicrobial treatment, prescriptions for each subject were ranked according to the sequence of prescription (as first, second, third, etc). Marginal Cox regression analysis\textsuperscript{15} was used to estimate effectiveness for each ranked endpoint: for example, comparing the incidence of having seventh prescription between the control and PHiD-CV10 groups. For each ranked endpoint analysis, factors used for stratified randomisation were included as explanatory variables and the overdispersion due to cluster-randomised design was accounted for by using the sandwich variance estimator.\textsuperscript{16}

Due to wide variation detected in the incidence of antimicrobial purchases in the trial clusters, we collected historical aggregate data for the birth cohort of 2006 (i.e. cohort not eligible for the trial participation) from birth up to 24 months of age. Incidence of purchases by cluster in those born in 2006 was used as an additional explanatory variable in explorative post hoc analyses to adjust the VE analyses for the background variation. Statistical analyses were performed with R version 3.0.1 and SAS software (version 9.22; SAS\textsuperscript{®}).

The study protocols were approved by the relevant ethical review boards and competent authorities before trial start. The full protocol is available at [www.finip.fi](http://www.finip.fi). This trial and nested AOM trial are registered at [ClinicalTrials.gov](https://clinicaltrials.gov), NCT00861380 and NCT00839254.

**Role of the funding source**

This collaborative study was mainly funded by GlaxoSmithKline Biologicals SA and co-funded by the National Institute for Health and Welfare (THL). Both parties were involved in all stages of the study planning, conduct, data collection, analyses and manuscript development. All authors had access to all the data and accepted responsibility for its validity. All authors agreed on the final decision to submit for publication.
RESULTS

We enrolled 47366 subjects in the 78 clusters between February 18, 2009 and October 5, 2010 (Figure 1). 45974 subjects who received correctly assigned vaccine were included in the ITT analyses.

The primary vaccination series was completed in 97 to 99% of subjects in the PHID-CV10 and control 3+1 and 2+1 infant cohorts. The mean follow-up was 24 months (range 14-34) for infants and 27 months (range 13-34) for subjects in the catch-up groups. The baseline and vaccination data have been presented earlier in detail.11

During the blinded ITT follow-up we identified a total of 148536 antimicrobial purchases. In the control group, the incidences of antimicrobial purchases ranged from 1·38 to 1·69 per person-year in the different age cohorts. Amoxicillin was the most common antimicrobial (39%) followed by amoxicillin with enzyme inhibitor (18%), azithromycin (16%), and sulfadiazine and trimethoprim (13%). Of all antimicrobial purchases, 91% represented antimicrobials recommended for AOM.

The VE of the PHID-CV10 against the outpatient purchases of antimicrobials recommended for AOM in the infant cohort was 8% (95% CI 1 to 14, table 1). The VE estimates for the 3+1 and 2+1 schedules were almost identical. Furthermore, the impact of both PHID-CV10 schedules was similar during the follow-up from the first dose: it started after three months and sustained at least up to 33 months of age (Figure 2).

The incidence rate difference of purchases of antimicrobials recommended for AOM was 0·12 per person-year (table 1). Thus, the NNV was 5 (95% CI 3 to 67) to prevent one purchase during the two-year follow-up.

The effectiveness of the vaccine in the infant cohort varied by the antimicrobial agent purchased (table 2). The point estimate was highest for amoxicillin with enzyme inhibitor (VE 16%, 0 to 30) and between 1 to 10% for other commonly used antimicrobials.

The indication for which the antimicrobial was prescribed was extractable from the prescription text for 52% of all prescriptions. However, the indication data were not evenly available across the study clusters (range 28-81%) and thus, these data could not be used for VE assessment. Nevertheless, out of the prescriptions with indication available, the most frequent indication was otitis media for 84% followed by other respiratory tract infections (10%). Antimicrobial prophylaxis was the indication in 2% of the prescriptions. The highest impact of the PHID-CV10 was seen outside the summer months with highest incidence compatible with epidemics of respiratory infections (Figure 3).

The number of outpatient purchases of antimicrobials recommended for AOM ranged from 0 to 30 per subject (median 2) during the ITT follow-up. The point estimates for the VE became greater with the increasing number of antimicrobial purchases per subject as the outcome. For example, the incidence rate of the 7th prescription on an individual was reduced by 16% (2 to 27) in the infant PHID-CV10 groups compared to the control group (Figure 4).

We noted considerable variation in the incidence of antimicrobial purchases between the study clusters from 1·16 to 2·14 per person-year in the infant control cohorts (Supplement figure 1). Therefore, we analysed pre-trial data on antimicrobial consumption for the 2006 birth cohort up to 24 months of age in the same clusters. These cluster-specific data highly correlated with the trial data (Supplement figure 2). Importantly, we observed no imbalance in the randomised clusters and the post hoc adjusted analyses with pre-trial data did not impact our VE estimates although the CIs were narrower in the adjusted analyses (Supplement table 1).

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Estimation of the VE in reducing the total DDD consumed and the costs of the antimicrobial purchases resulted in similar VE estimates (Supplement table 2).

For the catch-up cohorts, the VE estimates were lower and not statistically significant (table 1).
DISCUSSION

Our nationwide randomised trial showed reduction in outpatient antimicrobial purchases in PHiD-CV10 vaccinated children. Despite low estimates for relative VE, the absolute reduction was considerable due to the extensive load of antimicrobial use in the study population. Our analysis also suggests that the vaccine impact is greater in those most susceptible to infections as the VE estimates increased with the higher number of purchases per child. The vaccine impact started early after the first dose of the vaccine and sustained through to third year of life.

Earlier studies have demonstrated impact of the PCVs on antimicrobial consumption. Reduction of 5-4% (95% CI 4-0 to 6-7) was reported in the randomised, double-blind Northern California Kaiser Permanente (NCKP) trial after the first dose of the PCV7 3+1 schedule.17 In another randomised, double-blind trial18 15% reduction of illness episodes treated with antimicrobials (95% CI 3 to 25) in day-care attendees 12 to 35 months of age one month after two or one PCV9 doses was reported. A study from Italy19 reported a reduction of 11% in the number of antimicrobial courses (95% CI 6 to 17) in a non-randomised observational prospective cohort study of PCV7 2+1 schedule. However, the impact was seen only after the booster dose. In a retrospective study, a reduction of up to 42% for AOM diagnosis-related antimicrobial treatment has been reported when comparing time period after the vaccine implementation to time period before.20 Nearly 30% reduction in overall antimicrobial consumption was observed two years after PCV7 vaccination programme implementation. However, a subsequent study reported similar reduction already before the PCV7 programme but less impact after it. Of the studies evaluating the impact of PCV on the antimicrobial purchase rates, the Italian study19 reports age-specific incidences that are similar to the ones reported in this study. For other studies the incidences in the corresponding age groups are even higher than in the current study.

We consider our study data of high validity because of the randomised double-blind prospective trial design with concurrent controls. The outcome data were collected from an established nationwide register. All pharmacies in Finland are obliged to submit all purchased prescriptions to the register to get the state reimbursement for the medicines they have delivered. The benefits register of the Social Insurance Institution of Finland has collected data on outpatient antimicrobial purchases since 1995. We linked our trial data and the benefits register using the national unique Personal Identity Code, which is given to all permanent residents in Finland after birth or immigration and which remains unchanged through a person’s lifetime. Thus, we consider our detection of purchased antimicrobials for the study subjects close to complete.

The Finnish Current Care Guideline13 recommends antimicrobial treatment for definite diagnoses of AOM with amoxicillin as the primary choice. We selected purchases of the antimicrobials that are recommended for treatment of AOM in Finland as the primary endpoint for our analyses since they not only represent episodes of AOM, but also excellently reflect the burden caused by them to both the health care system and individuals. These antimicrobials comprised 91% of all antimicrobials purchased for outpatients, which is consistent with the several studies indicating that respiratory infections and especially AOM were known as the most common indications for antimicrobial prescriptions.2,6,7

We were not able to collect data related directly to otitis media diagnosis since the actual indication of the antimicrobial treatment was not systematically collected in the register. However, in half of the prescriptions the indication was written by the prescribing physician and otitis media was by far the most common indication found. Therefore, we feel that most of the reduction in antimicrobial use is due to a lower incidence on otitis media in the PHiD-CV10 vaccinated children. Furthermore, the incidence of antimicrobial treatment in the current trial was close to the incidence of AOM.

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Effect of PHiD-CV10 against antimicrobial purchases previously reported in Finland. However, it is also possible, that the vaccine prevented additionally other respiratory infections caused by pathogens preventable by PHiD-CV10.

The specificity of the antimicrobial purchase as an outcome for AOM, and especially pneumococcal AOM, may be poor for several reasons. First, the clinical diagnosis of AOM is difficult and overdiagnosis may occur. Second, the same antimicrobials are also prescribed for other diseases, also those with no pneumococcal aetiology, like tonsillitis and urinary tract infections. However, due to the double-blind randomised design the potential bias should be symmetric in the treatment groups. Furthermore, the low specificity of the outcome should bias the effectiveness estimates towards less effect. Therefore, the VE against true mucosal pneumococcal infections is probably considerably higher.

The clinical benefit of the antimicrobial use in the treatment of AOM has been recently confirmed in infants and young children. Antimicrobials are commonly recommended in many national guidelines and also routinely prescribed as the primary treatment for AOM. Despite active programs to reduce antimicrobial consumption they will continue serving as the cornerstone treatment for AOM, especially in children less than two years of age.

The results of this study should be directly generalizable to high income countries with similar high prescription rates for respiratory infections in children as the outcome data were collected from routine care during the trial. From public health perspective the reduction of antimicrobial consumption is important in terms of reduced treatment costs and prevention of the development of antimicrobial resistance. More than 12000 antimicrobial purchases and pharmacy costs alone of over 200000 € can be averted yearly in children under 24 months of age in Finland with a birth cohort of 60000.

In conclusion, the high burden of antimicrobial consumption combined with observed VE translates into an exceptionally high absolute reduction, and a low NNV to prevent one outcome (5 per two-year follow-up). This compares favourably to the IPD results from the same trial with NNV of more than 800 per two-year follow-up to prevent one case of culture-confirmed IPD. Due to a low relative and a high absolute effect, the impact of the vaccine on antimicrobial consumption will be more readily seen on population level rather than on individual subjects. However, further reduction of antimicrobial consumption should be pursued, especially by reducing inappropriate prescribing. This should be easier during the pneumococcal vaccination era when the most serious etiologic agent of secondary bacterial infection can be, at least partially, controlled.
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THL personnel contributing to the study:

**Study physicians** Susanna Pihlman, Ulla-Maija Rautakorpi, Ritva Syrjänen

**Study nurses** Päivi Sirén (head nurse), Sanna Huovari, Anni Huttunen, Susanna Jääskeläinen, Satu Karjalainen, Maila Kyrölä, Eija Lahtinen, Sanna Laine, Sini Lang, Anu-Riikka Markkanen, Seija Nieminen, Aune Niittyvuopio, Kaisu Riikonen, Tanja Trygg, Paula Vuorenniemi, Mari Vuorijärvi

**Data management** Piia Peltola, Jonas Sundman

**Media activities** Saima Pitkänen

**Secretariat** Ulla Johansson

**THL Steering committee members** Kari Auranen, Tarja Kaijala, Helena Käyhty, Hanna Nohyne, Petri Ruutu

GSK personnel contributing to the study:

**Study clinical operations** Liesbet de Cock, Raquel Merino, Paulo Negrier, Minna Neulasalmi, Markku Pulkkini, Satu Sumanen, Kaisa Kaitila

**Data management** Valerie Balosso, Fanny Naessens, Fabien Roux, Srilakshmi Pranesh

**Administrative assistance** Candice Collin, Severine Fanchon, Els De Kock,

**Medical writers** Liliana Manciu (protocol development), Bart van Heertum (manuscript coordination), Kristel Vercauteren (protocol and clinical study report development).

AUTHORS’ CONTRIBUTIONS:

A. palmu contributed to the concept and study design, acquisition of data, data analysis and interpretation, drafting of the manuscript, review and final approval of manuscript.

J. Jokinen contributed to the concept and study design, acquisition of data, statistical analysis, data interpretation, drafting of the manuscript, review and final approval of manuscript.

H. Nieminen contributed to acquisition of data, data interpretation, review and final approval of manuscript.

E. Ruokokoski contributed to the study design, acquisition of data, data interpretation, review and final approval of manuscript.

H. Rinta-Kokko contributed to the statistical analysis, data interpretation, review and final approval of manuscript.

T. Puumalainen contributed to the concept and study design, the study conduct, data analysis and interpretation, review and final approval of manuscript.

D. Borys contributed to the concept and study design, the study conduct, data analysis and interpretation, review and final approval of manuscript.

P. Lommel contributed to the study design, statistical analysis, data interpretation, review and final approval of manuscript.

M. Traskine contributed to statistical analysis, data interpretation, review and final approval of manuscript.

M. Moreira contributed to the study conduct, data interpretation, review and final approval of manuscript.

L. Schuereman contributed to the study design, data interpretation, review and final approval of manuscript.

T.M. Kilpi contributed to the concept and study design, acquisition of data, data analysis and interpretation, drafting of the manuscript, review and final approval of manuscript.

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CONFLICT OF INTEREST:

A.A. Palmu has had travel paid for and honoraria by GlaxoSmithKline group of companies to attend expert group meetings, has had travel paid by Merck to attend expert group meetings and has received a travel grant from SanofiPasteur MSD. He is the head of Clinical Research Unit at the National Institute for Health and Welfare, which has received research funding from GlaxoSmithKline group of companies.

J. Jokinen is the head of Vaccine Research Unit at the National Institute for Health and Welfare, which has received research funding from GlaxoSmithKline group of companies.

H. Nieminen is an employee of the Department of Vaccination and Immune Protection at the National Institute for Health and Welfare, which has received research funding from GlaxoSmithKline group of companies.

E. Ruokokoski is an employee of the Department of Vaccination and Immune Protection at the National Institute for Health and Welfare, which has received research funding from GlaxoSmithKline group of companies.

H. Rinta-Kokko is an employee of the Department of Vaccination and Immune Protection at the National Institute for Health and Welfare, which has received research funding from GlaxoSmithKline group of companies.

T. Puumalainen was an employee of GlaxoSmithKline group of companies during the study conduct.

D. Borys is an employee of GlaxoSmithKline group of companies and has stock and stock options ownership of GlaxoSmithKline group of companies.

P. Lommel is an employee of GlaxoSmithKline group of companies and has stock ownership of GlaxoSmithKline group of companies.

M. Traskine is an employee of GlaxoSmithKline group of companies.

M. Moreira is an employee of GlaxoSmithKline group of companies and has stock ownership of GlaxoSmithKline group of companies.

L. Schuerman is an employee of GlaxoSmithKline group of companies and has stock ownership of GlaxoSmithKline group of companies.

T.M. Kilpi is director of the Department of Vaccination and Immune Protection at the National Institute for Health and Welfare, which has received research funding from GlaxoSmithKline group of companies.

Synflorix, Engerix B and Havrix 720 Junior are trademarks of the GlaxoSmithKline group of companies. Prevenar/Prevnar is a trademark of Pfizer.
References


### Table 1. Outpatient purchases of prescribed antimicrobials and the vaccine effectiveness for the 10-valent PHiD-CV during intention-to-treat follow-up

<table>
<thead>
<tr>
<th>Endpoint definition and vaccinated cohort</th>
<th>Number of purchases</th>
<th>Follow-up time, person-years</th>
<th>Number of purchases per person-year</th>
<th>Number of purchases per person-year, cluster-specific averages</th>
<th>Vaccine effectiveness (VE)</th>
<th>Incidence rate difference</th>
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<td>Purchase of any outpatient antimicrobial, 3+1 and 2+1 schedule combined from dose 1</td>
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<td>34852</td>
<td>40423</td>
<td>20427</td>
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<td>31982</td>
<td>40423</td>
<td>20427</td>
<td>1.43</td>
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<tr>
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<td>31982</td>
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<tr>
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<td>31982</td>
<td>19793</td>
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</tr>
<tr>
<td>Purchase of antimicrobial recommended for AOM, Catch-up 12-18 months</td>
<td>17435</td>
<td>9097</td>
<td>14804</td>
<td>7156</td>
<td>1.18</td>
<td>3***</td>
</tr>
</tbody>
</table>

* antimicrobials recommended for treatment of acute otitis media by the national guideline**: amoxicillin with and without enzyme inhibitor, phenoxymethylpenicillin, cefuroxime, cefaclor, sulfadiazine and trimethoprim, clarithromycin, azithromycin

** VE 7.8% [95% CI -0.6 to 15.5] according to analysis done using SAS software (version 9.22; SAS®)

*** VE 3.5% [95% CI -4.6 to 10.9] according to analysis done using SAS software (version 9.22; SAS®)

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<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Number of purchases</th>
<th>Number of purchases per person-year, cluster-specific averages</th>
<th>Vaccine effectiveness (VE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PHiD-CV10 group, N=20327 subjects</td>
<td>Control group, N=10200 subjects</td>
<td>PHiD-CV10 group</td>
</tr>
<tr>
<td>Amoxicillin J01CA04*</td>
<td>25306</td>
<td>13781</td>
<td>0.622</td>
</tr>
<tr>
<td>Amoxicillin and enzyme inhibitor J01CR02*</td>
<td>10980</td>
<td>6673</td>
<td>0.275</td>
</tr>
<tr>
<td>Azithromycin J01FA10*</td>
<td>10364</td>
<td>5533</td>
<td>0.258</td>
</tr>
<tr>
<td>Sulfadiazine and trimethoprim J01EE02*</td>
<td>8845</td>
<td>4674</td>
<td>0.215</td>
</tr>
<tr>
<td>Cefalexin J01DB01</td>
<td>5207</td>
<td>2700</td>
<td>0.131</td>
</tr>
<tr>
<td>Clarithromycin J01FA09*</td>
<td>1326</td>
<td>715</td>
<td>0.031</td>
</tr>
<tr>
<td>Phenoxymethylpenicillin J01CE02*</td>
<td>805</td>
<td>395</td>
<td>0.020</td>
</tr>
<tr>
<td>Cefaclor or cefuroxime J01DC04, J01DC02*</td>
<td>668</td>
<td>377</td>
<td>0.016</td>
</tr>
<tr>
<td>Trimethoprim J01EA01</td>
<td>525</td>
<td>209</td>
<td>0.012</td>
</tr>
<tr>
<td>Others</td>
<td>22</td>
<td>22</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* antimicrobials recommended in the national guideline for treatment of AOM in Finland

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Figure legends

Figure 1: Trial profile

Figure 2. Incidence of outpatient purchases of antimicrobials recommended for AOM by treatment and age in children enrolled before 7 months of age

Figure 3. Incidence of outpatient purchases of antimicrobials recommended for AOM by calendar month in children enrolled before 7 months of age

Figure 4. Vaccine effectiveness against outpatient purchases of antimicrobials recommended for AOM by purchase episode rank in infants (N total 20327 in the PHiD-CV10 group and 10200 in the control group)
Effect of PHiD-CV10 against antimicrobial purchases

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Supplement table 1. **Outpatient purchases of prescribed antimicrobials and the vaccine effectiveness for the 10-valent PHiD-CV during intention-to-treat follow-up. Results obtained from explorative post hoc analyses using 2006 birth cohort data to adjust the VE analyses for the background variation detected in the study clusters.**

<table>
<thead>
<tr>
<th>Endpoint definition and vaccinated cohort</th>
<th>Number of purchases</th>
<th>Follow-up time, person-years</th>
<th>Number of purchases per person-year, cluster-specific averages</th>
<th>Vaccine effectiveness (VE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purchase of any outpatient antimicrobial, 3+1 and 2+1 schedule combined from dose 1</td>
<td>63584</td>
<td>34852</td>
<td>40423</td>
<td>20427</td>
</tr>
<tr>
<td>Purchase of antimicrobial recommended for AOM*, 3+1 and 2+1 schedule combined from dose 1</td>
<td>57964</td>
<td>31982</td>
<td>40423</td>
<td>20427</td>
</tr>
<tr>
<td>Purchase of antimicrobial recommended for AOM, 3+1 schedule from dose 1</td>
<td>24927</td>
<td>31982</td>
<td>21030</td>
<td>20427</td>
</tr>
<tr>
<td>Purchase of antimicrobial recommended for AOM, 2+1 schedule from dose 1</td>
<td>28027</td>
<td>31982</td>
<td>19793</td>
<td>20427</td>
</tr>
<tr>
<td>Purchase of antimicrobial recommended for AOM, Catch-up 7-11 months</td>
<td>12061</td>
<td>6474</td>
<td>8672</td>
<td>4317</td>
</tr>
<tr>
<td>Purchase of antimicrobial recommended for AOM, Catch-up 12-18 months</td>
<td>17435</td>
<td>9097</td>
<td>14804</td>
<td>7156</td>
</tr>
</tbody>
</table>

* antimicrobials recommended for treatment of acute otitis media by the national guideline (ref): amoxicillin with and without enzyme inhibitor, phenoxy methylpenicillin, cefuroxime, cefaclor, sulfadiazine and trimethoprim, clarithromycin, azithromycin

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Supplement table 2. *Outpatient antimicrobial consumption in DDDs, costs for all purchased doses and the vaccine effectiveness for the 10-valent PhID-CV during intention-to-treat follow-up*

<table>
<thead>
<tr>
<th>Endpoint definition and vaccinated cohort</th>
<th>Defined Daily Doses (DDD), per 1000 person-years per day</th>
<th>Vaccine effectiveness (VE)</th>
<th>Costs of the purchased antimicrobials, Euros (€) per person year</th>
<th>Vaccine effectiveness (VE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PHiD-CV10 group</td>
<td>Control group</td>
<td>VE point estimate (%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Purchase of any outpatient antimicrobial, 3+1 and 2+1 schedule combined from dose 1</td>
<td>13±9</td>
<td>15±0</td>
<td>7</td>
<td>1 to 13</td>
</tr>
<tr>
<td>Purchase of antimicrobial recommended for AOM*, 3+1 and 2+1 schedule combined from dose 1</td>
<td>12±7</td>
<td>13±8</td>
<td>8</td>
<td>1 to 14</td>
</tr>
<tr>
<td>Purchase of antimicrobial recommended for AOM, Catch-up 7-11 months</td>
<td>13±9</td>
<td>14±3</td>
<td>3</td>
<td>-6 to 12</td>
</tr>
<tr>
<td>Purchase of antimicrobial recommended for AOM, Catch-up 12-18 months</td>
<td>12±4</td>
<td>12±7</td>
<td>3</td>
<td>-5 to 11</td>
</tr>
</tbody>
</table>

* outpatient antimicrobials recommended for treatment of acute otitis media by the national guideline (ref): amoxicillin with and without enzyme inhibitor, phenoxymethylpenicillin, cefuroxime, cefaclor, sulfadiazine and trimethoprim, clarithromycin, azithromycin

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Supplement Figure 1: Distribution of any antimicrobial purchase incidences in the study clusters by vaccine group (N=26 per group) in infants

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Supplement Figure 2: Scatter plots of incidences of antimicrobial purchases in the FinIP infant cohorts and historical data from 2006 to 2008 by the study clusters (N=78). Historical and FinIP cohort incidences are not directly comparable because of different follow-up periods, but the figure shows the association between the two, as demonstrated by correlation coefficient.

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