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

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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

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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.[17] Another randomised trial with nine-valent conjugate vaccine given to children 12 to 35 months of age in day care centres was identified.[18] 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.[19] 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.[17] The low relative vaccine effectiveness estimates translate into considerable absolute public health impact due to the high incidence of antimicrobial use in children.

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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.

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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.

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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.[13] 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), sulfadiazine and trimethoprim (J01EE02), clarithromycin (J01FA09), and azithromycin (J01FA10).

Safety follow-up has been reported elsewhere.[11,12]

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.[11]

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.[14] 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[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.[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®).

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. This trial and nested AOM trial are registered at 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).

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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 trial[18] 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 Italy[19] 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[2] but less impact after it. Of the studies evaluating the impact of PCV on the antimicrobial purchase rates, the Italian study[19] 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 Guideline[13] 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

previously reported in Finland.[8] 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.[21,22] Antimicrobials are commonly recommended in many national guidelines[13] and also routinely prescribed as the primary treatment for AOM.[23] 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.[11] 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 pursuit, 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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AUTHORS' CONTRIBUTIONS:
A.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.
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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.
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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.
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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.

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References

1. Sabuncu E, David J, Bernède-Bauduin C, Pépin S, Leroy M, Boëlle PY, Watier L, Guillemot D. Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002-2007. PLoS Med 2009; **6:**e1000084.

2. Grijalva CG, Nuorti JP, Griffi n MR. Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. JAMA 2009; **302:** 758–66.

3. Bluestone CD, Stephenson JS, Martin LM. Ten-year review of otitis media pathogens. Pediatr Infect Dis J 1992; **11**: S7–11.

4. Kilpi T, Herva E, Kaijalainen T, et al. Bacteriology of acute otitis media in a cohort of Finnish children followed for the first two years of life. Pediatr Infect Dis J 2001; **20:** 654–62

5. Prymula R, Peeters P, Chrobok V, et al. Pneumococcal capsular polysaccharides conjugated to protein D provide protection against otitis media caused by both Streptococcus pneumoniae and nontypable Haemophilus influenzae: a randomized double blind efficacy study. *Lancet* 2006; **367:** 740–48.

6. Rautakorpi UM, Huikko S, Honkanen P, et al. The Antimicrobial Treatment Strategies (MIKSTRA) program: a 5-year follow-up of infection-specific antibiotic use in primary health care and the effect of implementation of treatment guidelines. Clin Infect Dis 2006 ;**42:** 1221–30.

7. Dommergues MA, Hentgen V. Decreased paediatric antibiotic consumption in France between 2000 and 2010. Scand J Infect Dis 2012; **44:** 495–501.

8. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001; **344:** 403–9.

9. Kilpi T, Ahman H, Jokinen J, et al. Protective efficacy of a second pneumococcal conjugate vaccine against pneumococcal acute otitis media in infants and children: randomized, controlled trial of a 7-valent pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine in 1666 children. Clin Infect Dis 2003; **37:** 1155–64.

10. Taylor S, Marchisio P, Vergison A, Harriague J, Hausdorff WP, Haggard M. Impact of pneumococcal conjugate vaccination on otitis media: a systematic review. Clin Infect Dis 2012; **54:** 1765–73.

11. Palmu AA, Jokinen J, Borys D, Nieminen H, Ruokokoski E, Siira L, Puumalainen T, Lommel P, Hezareh M, Moreira M, Schuerman L, Kilpi TM. Effectiveness of the ten-valent pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV10) against invasive pneumococcal disease: a cluster randomised trial. Lancet 2013; **381:** 214–22.

12. Timo Vesikari, Aino Forstén, Ilkka Seppä, et al. Immunogenicity and safety of 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in healthy finnish infants and toddlers. ESPID 2013, Milan, Italy, May 28 to June 1, 2013.

First published in The Lancet Infectious Diseases 2013 Nov 26 dx.doi.org/10.1016/S1473-3099(13)70338-4

13. Working group appointed by the Finnish Medical Society Duodecim, the Finnish Paediatric Society, the Finnish Otolaryngological Society and the Finnish Association for General Practice. Otitis media (acute). Current Care guideline. Finnish Medical Society Duodecim, Helsinki 2010. www.kaypahoito.fi accessed on July 2, 2013.

14. Donner A, Klar N. Design and analysis of cluster randomization trials in health research. Arnold. London 2000.

15. Wei LJ, Lin DY, Weissfeld L: Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. J Am Stat Assoc 1989; **84:** 1065–73.

16. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. J Am Stat Assoc 1989; **82:**1075–8.

17. Fireman B, Black SB, Shinefield HR, Lee J, Lewis E, Ray P. Impact of the pneumococcal conjugate vaccine on otitis media. Pediatr Infect Dis J 2003; **22:** 10–6.

18. Dagan R, Sikuler-Cohen M, Zamir O, Janco J, Givon-Lavi N, Fraser D. Effect of a conjugate pneumococcal vaccine on the occurrence of respiratory infections and antibiotic use in day-care center attendees. Pediatr Infect Dis J 2001; **20:** 951–8.

19. Esposito S, Lizioli A, Lastrico A, et al. Impact on respiratory tract infections of heptavalent pneumococcal conjugate vaccine administered at 3, 5 and 11 months of age. Respir Res 2007; **8:** 12. doi:10.1186/1465-9921-8-12

20. Zhou F, Shefer A, Kong Y, Nuorti JP. Trends in acute otitis media-related health care utilization by privately insured young children in the United States, 1997-2004. Pediatrics 2008; **121:** 253–60. doi: 10.1542/peds.2007-0619.

21. Tähtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A. A placebo-controlled trial of antimicrobial treatment for acute otitis media. N Engl J Med 2011; **364:** 116–26.

22. Hoberman A, Paradise JL, Rockette HE, Shaikh N, Wald ER, Kearney DH, Colborn DK, Kurs-Lasky M, Bhatnagar S, Haralam MA, Zoffel LM, Jenkins C, Pope MA, Balentine TL, Barbadora KA. Treatment of acute otitis media in children under 2 years of age. N Engl J Med 2011; **364:** 105–15.

23. Arguedas A, Kvaerner K, Liese J, Schilder AG, Pelton SI. Otitis media across nine countries: disease burden and management. Int J Pediatr Otorhinolaryngol 2010; **74:** 1419–24.

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

	Number of purchases		Follow-up time, person-years		Number of purchases per person-year		Number of purchases per person-year, cluster-specific averages		Vaccine effectiveness (VE)		Incidence rate difference	
Endpoint definition and vaccinated cohort	PHiD-CV10 group	Control group	PHiD-CV10 group	Control group	PHiD-CV10 group	Control group	PHiD-CV10 group	Control group	VE point estimate (%)	95% CI	Reduction per person-year	95% CI
Purchase of any outpatient antimicrobial, 3+1 and 2+1 schedule combined from dose 1	63584	34852	40423	20427	1•57	1•71	1•57	1•69	7	1 to 13	0•12	0•01 to 0•23
Purchase of antimicrobial recommended for AOM*, 3+1 and 2+1 schedule combined from dose 1	57964	31982	40423	20427	1•43	1•57	1•43	1•55	8	1 to 14	0•12	0•01 to 0•23
Purchase of antimicrobial recommended for AOM, 3+1 schedule from dose 1	29937	31982	20630	20427	1•45	1•57	1•43	1•55	8	-1 to 15	0•12	-0•01 to 0•24
Purchase of antimicrobial recommended for AOM, 2+1 schedule from dose 1	28027	31982	19793	20427	1•42	1•57	1•43	1•55	8	0 to 15**	0•12	-0•01 to 0•25
Purchase of antimicrobial recommended for AOM, Catch-up 7-11 months	12061	6474	8672	4317	1•39	1•50	1•43	1•46	4	-5 to 12	0•05	-0•07 to 0•17
Purchase of antimicrobial recommended for AOM, Catch-up 12-18 months	17435	9097	14804	7156	1•18	1•27	1•20	1•23	3***	-5 to 11	0•04	-0•05 to 0•12

* antimicrobials recommended for treatment of acute otitis media by the national guideline[13]: 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 2. Outpatient purchases of different antimicrobial agents and the vaccine effectiveness for the 10-valent PHiD-CV during intention-to-treat follow-up in infant 3+1 and 2+1 schedules combined

	Number of purchases		Number of purchases per person-year, cluster-specific averages		Vaccine effectiveness (VE)	
Antimicrobial agent	PHiD-CV10 group, N=20327 subjects	Control group, N=10200 subjects	PHiD-CV10 group	Control group	VE point estimate (%)	95% CI
Amoxicillin J01CA04*	25306	13781	0•622	0•672	8	3 to 13
Amoxicillin and enzyme inhibitor J01CR02*	10980	6673	0•275	0•324	16	0 to 29
Azithromycin J01FA10*	10364	5533	0•258	0•267	4	-9 to 16
Sulfadiazine and trimethoprim J01EE02*	8845	4674	0•215	0•223	4	-13 to 19
Cefalexin J01DB01	5207	2700	0•131	0•134	3	-9 to 14
Clarithromycin J01FA09*	1326	715	0•031	0•033	2	-24 to 23
Phenoxymethylpenicillin J01CE02*	805	395	0•020	0•021	1	-20 to 19
Cefaclor or cefuroxime J01DC04, J01DC02*	668	377	0•016	0•017	10	-28 to 37
Trimethoprim J01EA01	525	209	0•012	0•009	-39	-109 to 7
Others	22	22	0•001	0•001	49	-13 to 77

***** antimicrobials recommended in the national guideline for treatment of AOM in Finland[13]

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)

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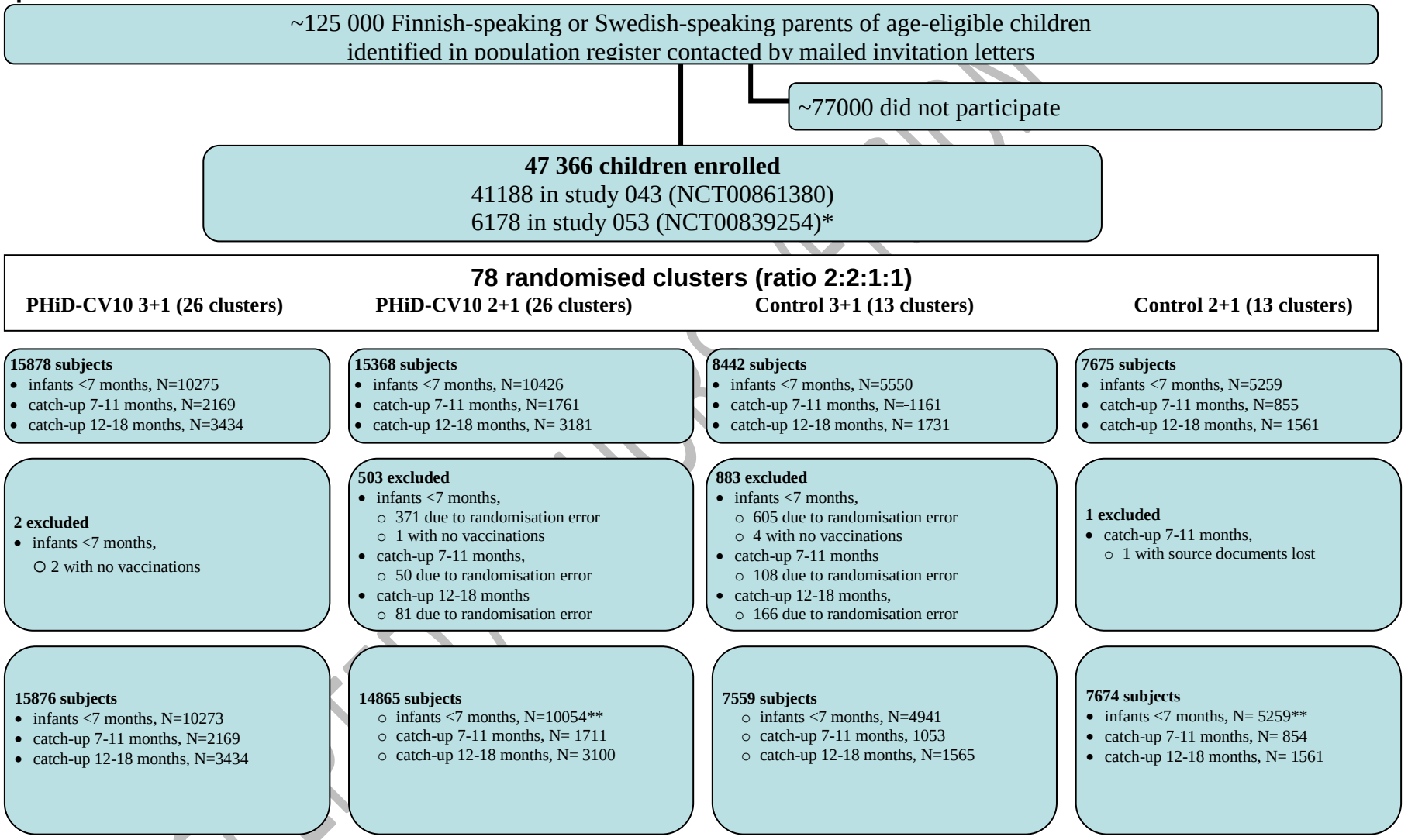
Figure 1: **Trial profile**



* 3 subjects not randomised nor vaccinated, ** includes one subject withdrawn from the register follow-up during the blinded follow-up period

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

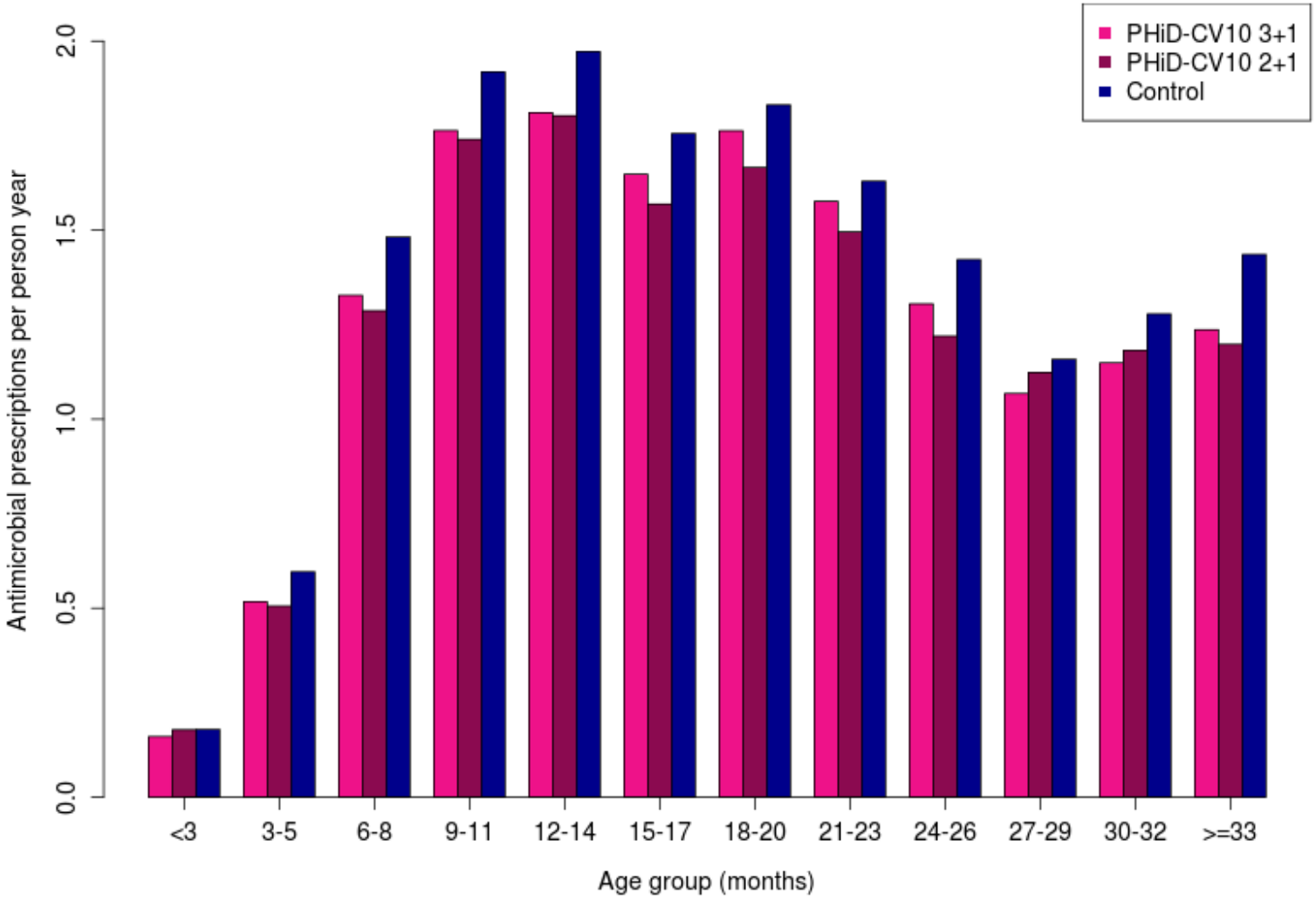

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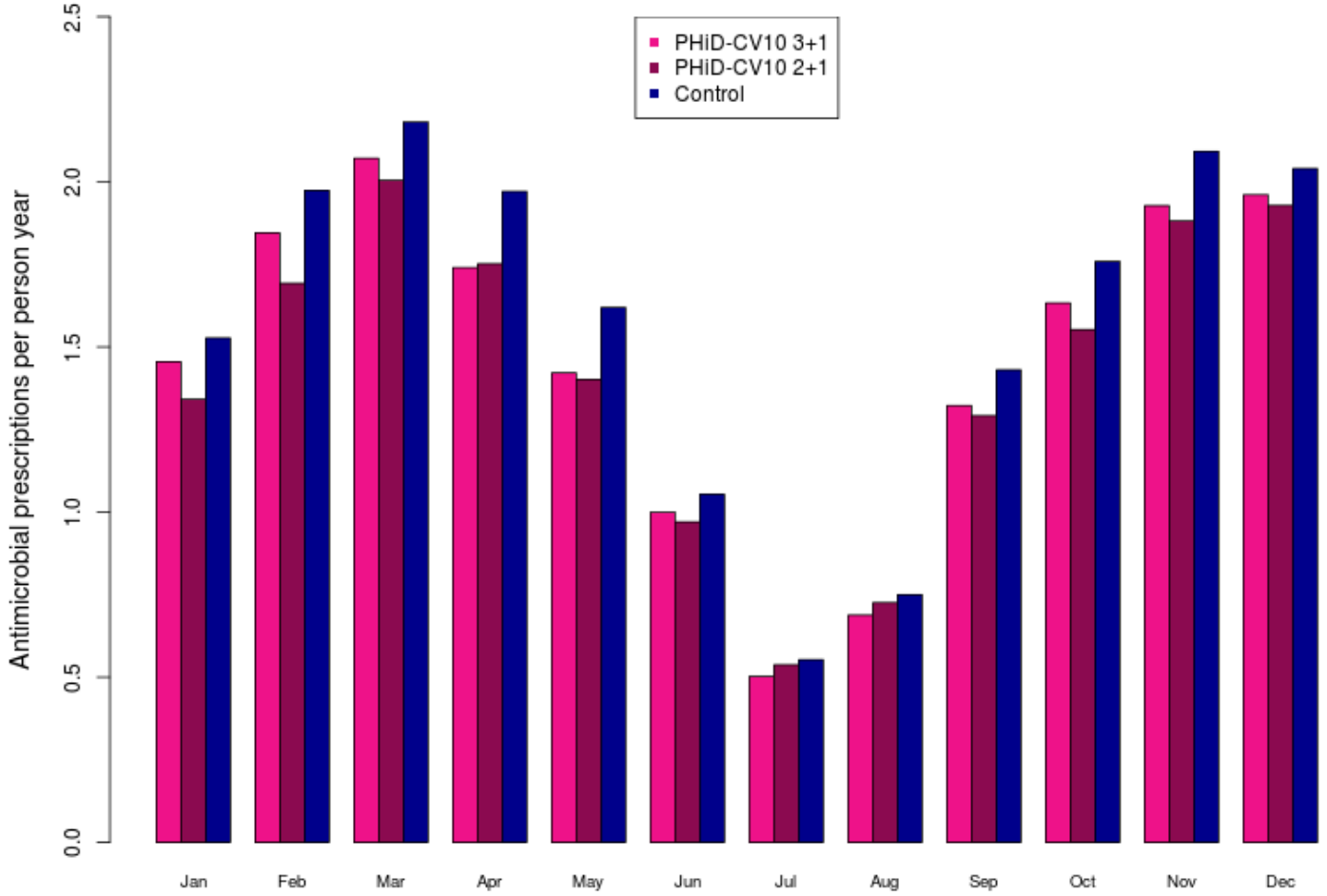
Figure 3. Incidence of outpatient purchases of antimicrobials recommended for AOM by calendar month in children enrolled before 7 months of age



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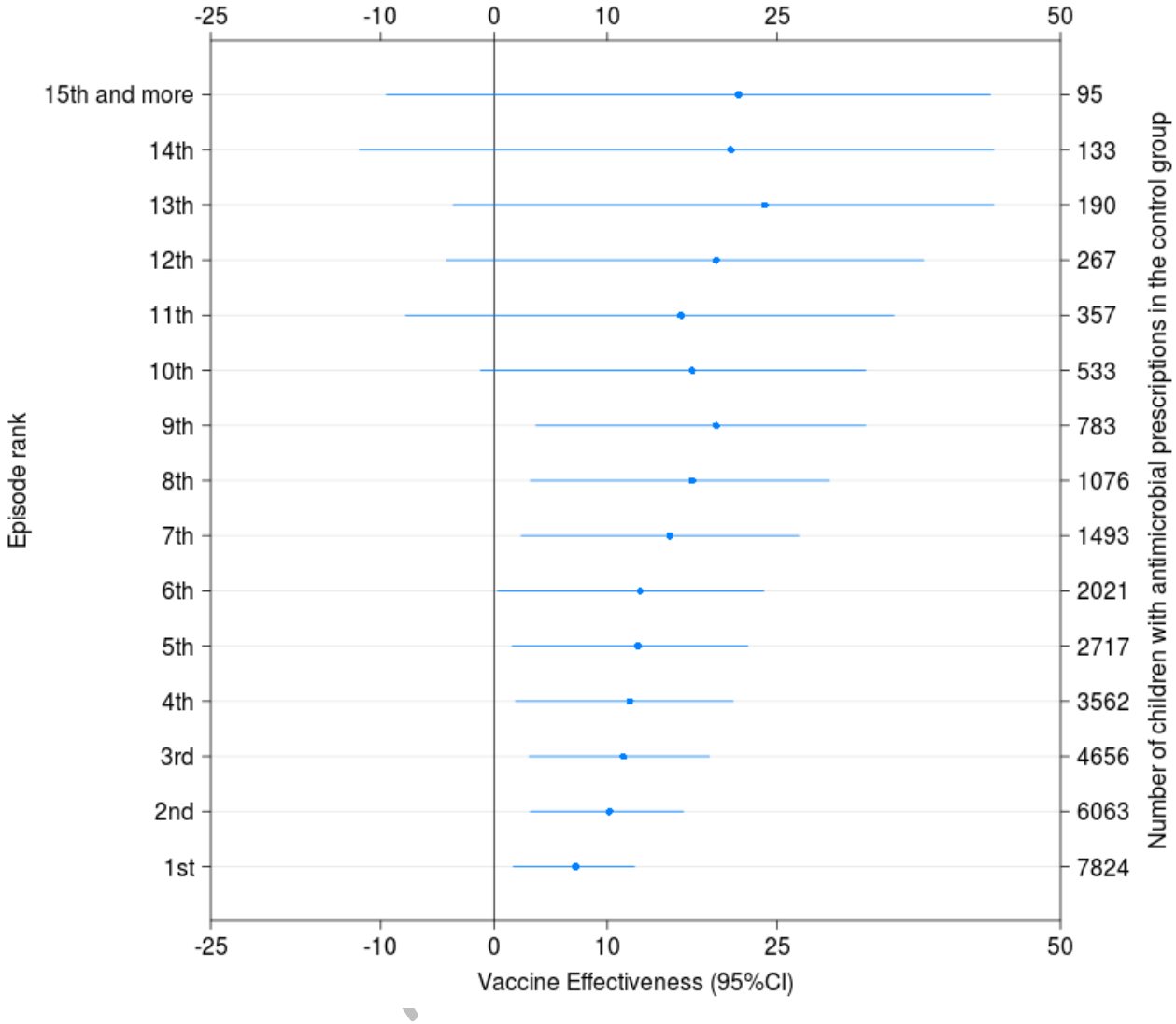

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Supplement table 1**. Outpatient purchases of prescribed antimicrobials and the vaccine effectiveness for the 10-valent PHiD-CV during intention-to-treat follow-up. Results obtained from explorative post hoc analyses using 2006 birth cohort data to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

	Number of purchases		Follow-up time, person-years		Number of purchases per person-year, cluster-specific averages		Vaccine effectiveness (VE)	
Endpoint definition and vaccinated cohort	PHiD-CV10 group	Control group	PHiD-CV10 group	Control group	PHiD-CV10 group	Control group	VE point estimate (%)	95% CI
Purchase of any outpatient antimicrobial, 3+1 and 2+1 schedule combined from dose 1	63584	34852	40423	20427	1•57	1•69	8	4 to 12
Purchase of antimicrobial recommended for AOM*, 3+1 and 2+1 schedule combined from dose 1	57964	31982	40423	20427	1•43	1•55	9	4 to 13
Purchase of antimicrobial recommended for AOM, 3+1 schedule from dose 1	29937	31982	20630	20427	1•43	1•55	7	2 to 12
Purchase of antimicrobial recommended for AOM, 2+1 schedule from dose 1	28027	31982	19793	20427	1•43	1•55	10	5 to 15
Purchase of antimicrobial recommended for AOM, Catch-up 7-11 months	12061	6474	8672	4317	1•43	1•46	4	-3 to 11
Purchase of antimicrobial recommended for AOM, Catch-up 12-18 months	17435	9097	14804	7156	1•12	1•23	4	-3 to 10

* 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 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**

	Defined Daily Doses (DDD), per 1000 person-years per day		**Vaccine effectiveness (VE)**		**Costs of the purchased antimicrobials, Euros (€) per person year**		**Vaccine effectiveness (VE)**	
Endpoint definition and vaccinated cohort	PHiD-CV10 group	Control group	VE point estimate (%)	95% CI	PHiD-CV10 group	Control group	VE point estimate (%)	95% CI
Purchase of any outpatient antimicrobial, 3+1 and 2+1 schedule combined from dose 1	13•9	15•0	7	1 to 13	20•2	22•1	8	2 to 15
Purchase of antimicrobial recommended for AOM*, 3+1 and 2+1 schedule combined from dose 1	12•7	13•8	8	1 to 14	18•3	20•2	9	2 to 16
Purchase of antimicrobial recommended for AOM, Catch-up 7-11 months	13•9	14•3	3	-6 to 12	19•2	19•6	3	-7 to 12
Purchase of antimicrobial recommended for AOM, Catch-up 12-18 months	12•4	12•7	3	-5 to 11	16•6	17•4	4	-4 to 12

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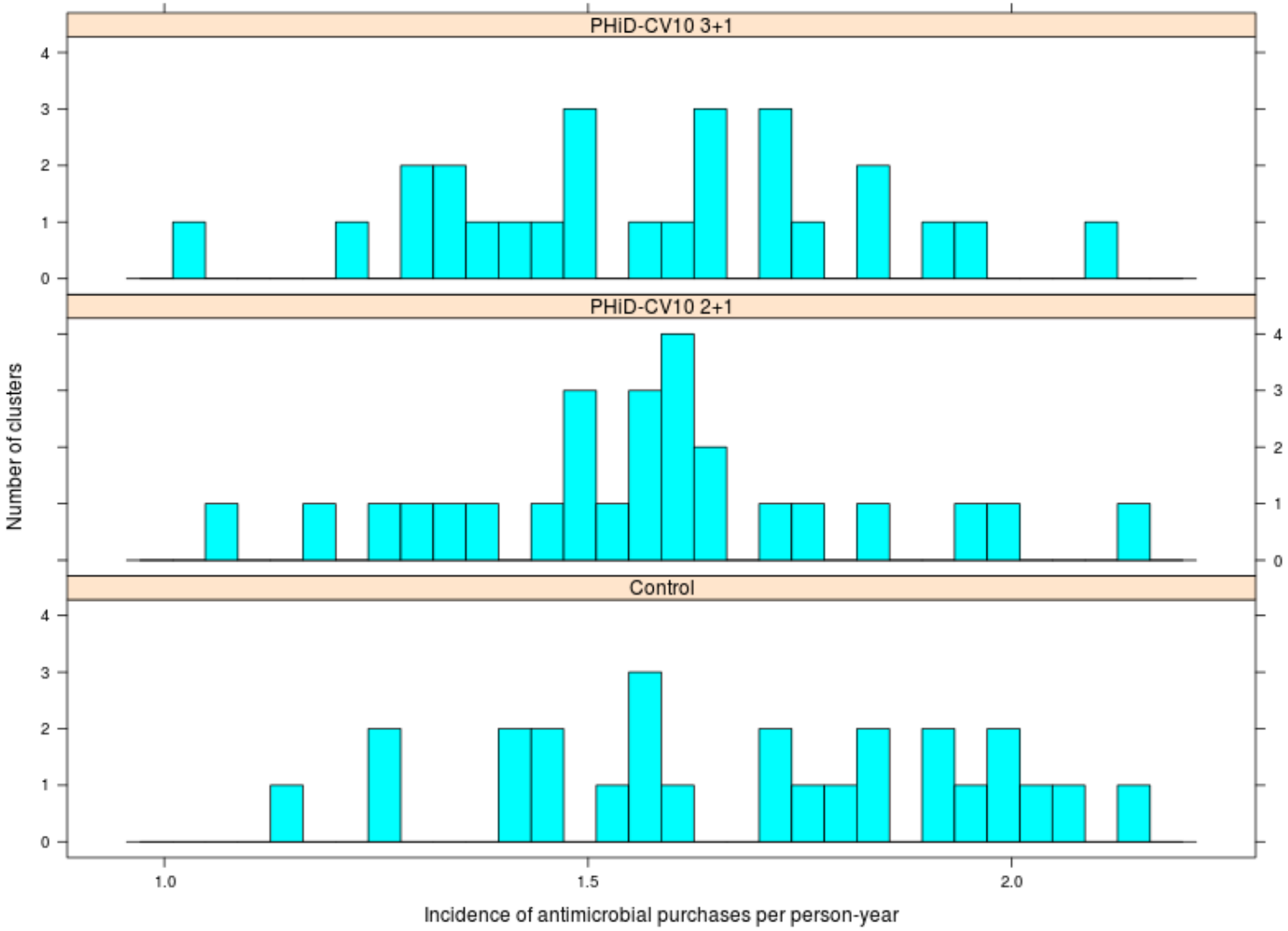
Supplement Figure 1: Distribution of any antimicrobial purchase incidences in the study clusters by vaccine group (N=26 per group) in infants



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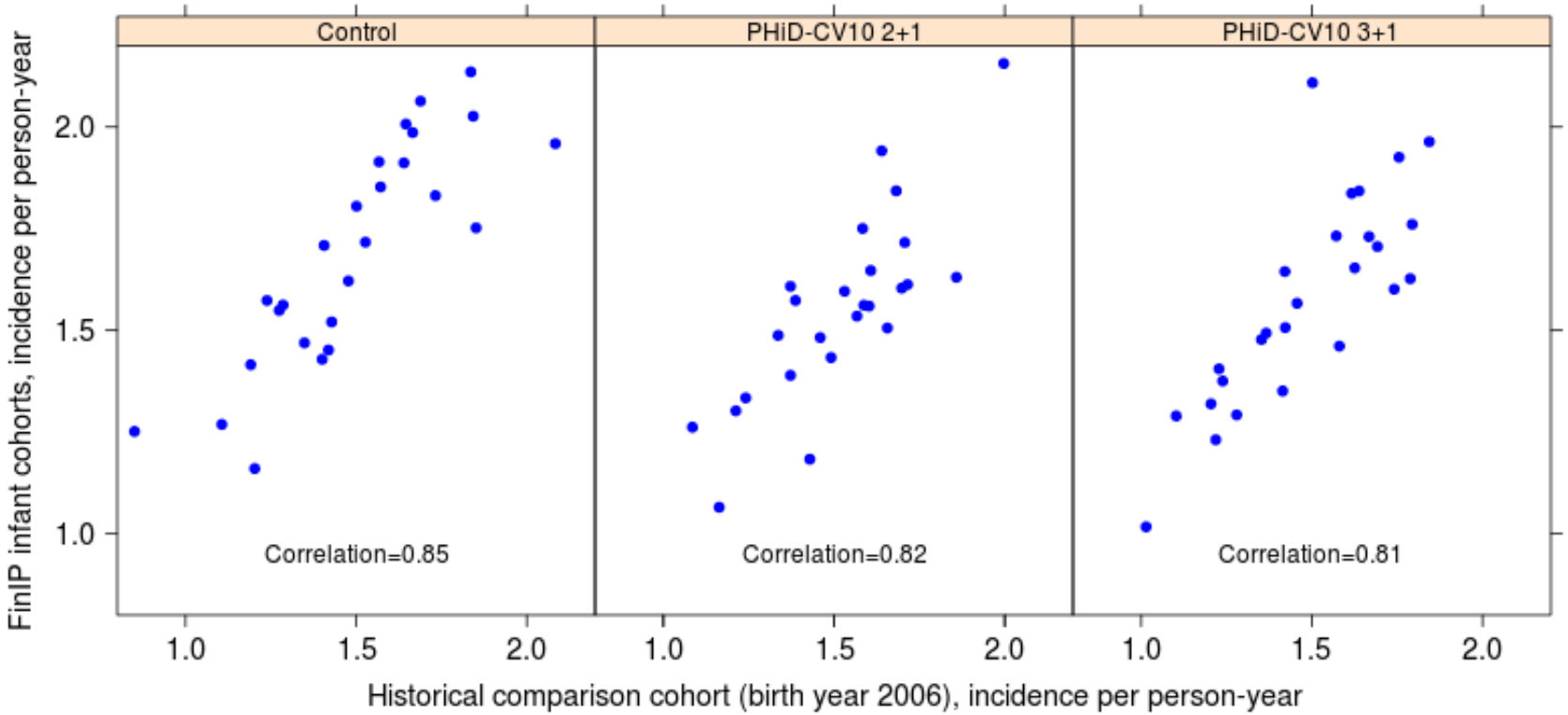
Supplement Figure 2: Scatter plots of incidences of antimicrobial purchases in the FinIP infant cohorts and historical data from 2006 to 2008 by the study clusters (N=78). Historical and FinIP cohort incidences are not directly comparable because of different follow-up periods, but the figure shows the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



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