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Decline in Early Childhood Respiratory Tract Infections in the Norwegian Mother and Child Cohort Study after Introduction of Pneumococcal Conjugate Vaccination

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Abstract

BACKGROUND—The seven-valent pneumococcal conjugate vaccine (PCV7) was introduced into the Norwegian Childhood Immunization Program in 2006. A substantial effectiveness of PCV7 immunization against invasive pneumococcal disease has been demonstrated, while evidence of the impact on respiratory tract infections are less consistent.

METHODS—This study included children participating in the Norwegian Mother and Child Cohort Study, which recruited pregnant women between 1999 and 2008. Maternal report of acute otitis media (AOM), lower respiratory tract infections (LRTIs) and asthma in the child was compared with PCV7 immunization status, as obtained from the Norwegian Immunization Registry. Generalized linear models with the log link function were used to report adjusted relative risks (RR) and 95% confidence intervals (CI).

RESULTS—For children who had received three or more PCV7 immunizations by 12 months of age, the adjusted relative risks of AOM and LRTIs between 12 and 18 months were 0.86 [95% CI: 0.81, 0.91] and 0.78 [95% CI: 0.70, 0.87] respectively, when compared with non-immunized children. A reduced risk of AOM, RR 0.92 [95% CI: 0.90, 0.94], and LRTIs, RR 0.75 [95% CI:

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0.71, 0.80], between 18 and 36 months of age was also identified among children who had received 3 or more immunizations by 18 months. No association was seen between PCV7 immunization and asthma at 36 months of age.

CONCLUSION—Reduced incidence proportions of AOM and LRTIs before 36 months of age were observed among children immunized with PCV7 through the childhood immunization program.

Keywords

Pneumococcal conjugate vaccination; lower respiratory tract infections; acute otitis media; asthma

Introduction

The disease burden caused by *Streptococcus pneumoniae* is high, the bacterium being one of the most common pathogens responsible for bacterial pneumonia, meningitis and sepsis¹. Pneumonia is the primary cause of morbidity and mortality worldwide, and *S. pneumoniae* is the etiologic agent in 17–40% of pneumonia related hospitalizations in children^{2,3}. Although it is less severe, acute otitis media (AOM) is exceedingly common, driving the use of antibiotics and leading to substantial public costs. *S. pneumoniae* is estimated to account for 30–55% of AOM episodes in preschool aged children^{4,5}. The 23-valent pneumococcal polysaccharide vaccine (PPV23) is not immunogenic in children younger than 24 months, which prompted the development of an alternative pneumococcal vaccine⁶. The seven-valent pneumococcal conjugate vaccine (PCV7), first licensed in the United States in 2000, is immunogenic in children younger than 24 months of age⁷. This vaccine includes the seven serotypes responsible for most invasive pneumococcal disease (IPD) in developed countries, i.e. serotypes 4, 6B, 9V, 14, 18C, 19F and 23F⁸.

Pneumococcal conjugate vaccines have been licensed in more than 90 countries and incorporated into the immunization program of 26 countries⁹, based on their high efficacy in reducing IPD among children younger than 24 months of age in randomized controlled trials^{8,10–12}, in addition to a moderate efficacy against pneumonia^{10,11,13–15} and AOM^{5,8,16–19}. Few adverse reactions to the pneumococcal conjugate vaccines have been recorded, but a South African trial identified an increase in hospital admissions due to asthma symptoms among immunized children¹¹. In contrast, PCV7 immunization seemed to suppress the hallmark features of asthma in a mouse model²⁰. Post licensure studies examining pneumococcal conjugate vaccination and development of AOM and pneumonia have been ecologic in nature, primarily based on surveillance registries and insurance claims databases^{21–25}. These studies have therefore not had available individual data on both immunization status and health outcomes.

PCV7 was introduced into the Norwegian Childhood Immunization Program in July 2006, following a 2 +1 dose schedule, with two primary immunizations at 3 and 5 months, and a booster dose at 12 months of age. Catch-up vaccination was conducted of all children born in 2006. Pneumococcal immunization of children younger than 24 months before 2006 was negligible. Vaccine uptake increased rapidly, and by January 2008, 80% of children less than 13 months of age had received three immunizations²⁶. The vaccine effectiveness against IPD was 74% in the Norwegian population younger than 24 months²⁶.

The Norwegian Mother and Child Cohort Study (MoBa) is a pregnancy cohort administered by the Norwegian Institute of Public Health. Pregnant women were recruited from all over Norway between 1999 and 2008. The objective of the current study was to assess the impact of PCV7 immunization by comparing maternal report of AOM, lower respiratory tract infections (LRTIs) and asthma among immunized and non-immunized children.

Materials and methods

The Norwegian Mother and Child Cohort study

MoBa is a prospective pregnancy cohort study that has been described in detail elsewhere^{27,28}. Briefly, pregnant women were recruited at approximately 18 weeks gestation, from 39 of 50 maternity units in Norway with more than 100 births annually. The participation rate of all invited pregnant women was 38.5%. The current study used version VI of the quality assured data files. The cohort includes 90,681 mothers. A written informed consent was obtained from all mothers. As mothers are allowed to participate with more than one child, the cohort includes 108,863 children. The questionnaires used in the current study were completed at the time of recruitment, around 18 gestational weeks (Q1), at 30 gestational weeks (Q3), and when the child was 6 (Q4), 18 (Q5), and 36 months old (Q6). The questionnaires are available online²⁹. All children from multiple births were excluded (N=3,801). The data from MoBa were linked to the Medical Birth Registry of Norway (MBRN) and the Norwegian Immunization Registry (SYSVAK) through 11-digit person identification numbers. Children who were not successfully linked to both registries were excluded (n=1,784), leaving 103,278 children, including 14,513 groups of siblings. This study was approved by the Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics.

Respiratory disorders

The outcomes of interest were AOM, LRTIs and asthma, as reported by mothers through MoBa questionnaires. Disease experienced when the child was <6 months of age, >6 months and <18 months, and >18 months and <36 months was reported at 6, 18 and 36 months of age, respectively. LRTIs was defined as an affirmative answer to a question asking whether the child had experienced pneumonia, bronchitis, and/or infections with respiratory syncytial virus before 18 months of age, and as an affirmative answer to a question of whether the child had experienced pneumonia and/or bronchitis between 18 and 36 months of age. The primary question asked did not distinguish whether this diagnosis had been verified by a doctor.

Year of Birth and Immunization status

The exposures of interest were year of birth (before 2006, 2006 and 2007, and 2008 and after), as registered in MBRN, and number of PCV7 immunizations, as registered in SYSVAK. The total number of PCV7 immunizations received by 12 and 18 months of age was categorized as 0, 1, 2, and 3 or more immunizations.

Measure of other covariates—Information on maternal and child characteristics hypothesized to be associated with both immunization status and the respiratory outcomes, based on knowledge of the literature, was gathered. Maternal age at delivery, parity, in addition to season of birth was obtained from the MBRN. The mother's highest completed educational level early in pregnancy, daily smoking during pregnancy, as well as daily smoking when the child was 6 and 18 months, were obtained through MoBa questionnaires. Data on duration of breastfeeding, age at start of day care attendance, hours spent in day care each week at 18 months and number of children the child was with during the day at 18 months, was obtained from MoBa questionnaires. The child's age in days at each immunization was gathered from SYSVAK.

Statistical analysis

First, differences in development of respiratory disorders were examined by year of birth. This phase included all the children with information available from the questionnaires at

the specific ages, including 86,306 at 6 months, 64,311 at 18 months and 49,635 at 36 months of age (See Figure, Supplementary Digital Content 1, <http://links.lww.com/INF/B239>). As few MoBa children were born in 1999 and 2000, and children born in 2009 had not reached 36 months at the time of the current study, incidence of disease was plotted for birth years 2001 to 2008. The Cuzick nonparametric test for trend was used to examine differences in the incidence of disease across birth year. Second, children with complete follow up information at 18 months were included when examining the association between number of PCV7 immunizations at 12 months of age and development of AOM and LRTIs between 12 and 18 months of age. Children immunized with PPV23 before 18 months (n=207) and children who had received a dose of PCV7 between 12 and 18 months (n=1,175) were excluded, leaving 58,274 children. Children with complete follow up information at 36 months of age were included when examining the association between number of PCV7 immunizations by 18 months and AOM and LRTIs between 18 and 36 months, in addition to current asthma at 36 months. Children immunized with PPV23 before 36 months (n=185) and children who had received a PCV7 dose between 18 and 36 months were excluded (n=562), leaving 42,672 children.

Generalized Linear Models (GLM) were fitted for each outcome using the log link function, reporting relative risks (RR) and 95% confidence intervals (CI), adjusting for all covariates associated with both the exposure and the outcome. Robust variance estimations with cluster adjustments were used to account for siblings. The primary multivariable analysis was a complete case analysis, where approximately 10% of observations had missing information on one or more of the covariates. Multivariable analysis was also conducted using multiple imputation by chained equations generating 10 imputations³⁰. A two sided 5% significance level was used for all tests and comparisons. The analysis was conducted in STATA version 11 (STATA, College Station, Texas, USA).

Results

Characteristics of children immunized with PCV7

By 18 months of age, 1.2% had received one immunization, 3.8% had received two immunizations and 38.3% had received three PCV7 immunizations. A total of 99.1% of the non-immunized children were born before 2006. A total of 15.0% of the children who had received one immunization, 35.6% of children who had received two immunizations and 96.2% of children who had received three or more immunizations were born in 2006 or after. The children who had received three or more immunizations before 18 months of age had followed the recommended immunization program, for whom median age at dose 1, 2, and 3 was 96, 164 and 373 days respectively. Mothers of immunized children were older, had a higher educational level, had a lower parity, and were less likely to have smoked during pregnancy, when compared to the non-immunized children. Immunized children were more likely to have been born in the south-east region of Norway, to attend day care before 9 months of age, spent more hours in day care at 18 months of age, and were together with more children during the day (See Table, Supplemental Digital Content 2, <http://links.lww.com/INF/B240>).

Incidence of respiratory disorders by year of birth

The incidence of AOM by year of birth showed a gradual downward trend, with test for trend p-values <0.001 for disease reported at 6, 18 and 36 months of age (See Figure, Supplemental Digital Content 3, <http://links.lww.com/INF/B241>). The incidence of AOM between 12 and 18 months was 22.4% among children born before 2006, 21.2% among children born in 2006 and 2007, and 19.5% among children born in 2008 and later, while the incidence of AOM between 18 and 36 months was 43.4% among children born before 2006,

41.0% for children born in 2006 and 2007, and 41.7% for children born in 2008 and later (See Tables, Supplemental Digital Content 4 and 5, <http://links.lww.com/INF/B242> and <http://links.lww.com/INF/B243>) The incidence of LRTIs reported at 36 months decreased among children born in 2005 and after, while the incidence of LRTIs reported at 18 months decreased for children born in 2006 and after, with test for trend p-values <0.001 for disease reported at 6, 18 and 36 months (See Figure, Supplemental Digital Content 6, <http://links.lww.com/INF/B245>). The incidence of LRTIs between 12 and 18 months of age was 8.8% among children born before 2006, 7.6% among children born in 2006 and 2007, and 7.2% among children born in 2008 and later, while the incidence of LRTIs between 18 and 36 months was 14.5% among children born before 2006, 11.0% among children born in 2006 and 2007 and 12.1% among children born in 2008 and later (See Tables, Supplemental Digital Content 4 and 5, <http://links.lww.com/INF/B242> and <http://links.lww.com/INF/B243>). Notably, the proportion of children with current asthma at 36 months remained stable, test for trend p-value 0.098 (See Figure, Supplemental Digital Content 7, <http://links.lww.com/INF/B246>).

Association between PCV7 immunization and respiratory disorders

Children who had received three PCV7 immunizations by 12 months of age had a reduced relative risk of AOM, RR 0.86 [95% CI: 0.81, 0.91], and LRTIs, RR 0.78 [95% CI: 0.70, 0.87], between 12 and 18 months of age after adjustment for identified confounders (Table 1). These inverse associations persisted, and children who had received three immunizations by 18 months of age had a reduced relative risk of AOM, RR 0.92 [95% CI: 0.90, 0.94], and LRTIs, RR 0.75 [95% CI: 0.71, 0.80], between 18 and 36 months of age after multivariable adjustment (Table 2). Maternal age, region of birth and age at start of day care attendance were the most important confounding factor identified, but only small changes in the estimates were observed. Similar tendencies were seen for children who had received two immunizations at the respective ages, while no associations were seen for children who had received only one. There was no association between PCV7 immunization and asthma at 36 months of age. A sensitivity analysis was conducted excluding non-immunized children born in 2006 and after, examining the potential influence of an indirect effect on the associations, yielding identical estimates as the primary analysis (data not shown).

Discussion

The present study describes a declining incidence of respiratory tract infections before 36 months by year of birth, starting around the time that PCV7 was introduced into the Norwegian Childhood Immunization Program. Furthermore, a reduced risk of AOM and LRTIs before 36 months of age was found among children who had followed the 2+1 PCV7 immunization schedule. These findings are of great public health importance due to the large disease burden among this age group.

The efficacy of PCV7 immunization in prevention of AOM and pneumonia has been shown through randomized controlled trials. A 7% reduction of all AOM episodes in the Kaiser Permanente trial⁸, and a non significant 6% reduction of all AOM episodes was demonstrated in a Finnish trial⁵. Furthermore, radiologically confirmed pneumonia was reduced by 18% in the Kaiser Permanente trial using WHO disease classification criteria¹⁴. However, the effectiveness of vaccines following implementation into immunization programs may differ from that observed in randomized controlled trials.

National rates of ambulatory visits for AOM in the United States before and after the introduction of PCV7 immunization in 2000 indicated a 20% reduction in outpatient medical visits for AOM among children younger than 24 months²¹. This is consistent with data from birth cohorts in Tennessee and New York indicating a 17% and 28% decrease in recurrent

otitis media, respectively²⁴. A study from Quebec, Canada, where PCV7 immunization of all children younger than 5 years of age was initiated in December 2004, indicated a 13.2% decrease in physician claims for AOM by 2007²⁵. In the present study, all-cause AOM was reported by mothers, irrespective of physician verification of the diagnosis. The 14% relative reduction of AOM between 12 and 18 months of age among fully immunized children is higher than findings from clinical trials, but comparable to that described in Quebec.

The impact of PCV7 immunization on all-cause pneumonia among children younger than 24 months in the United States was demonstrated through a 39% decline in hospital admission rates by 2004²². In the United Kingdom, where PCV7 was introduced in September 2006, nationwide hospital admissions for bacterial pneumonia and empyema showed a 19% and 22% decrease by 2008, respectively²³. In the present study, the risk of LRTIs among children who had received three or more immunizations was reduced by 22% between 12 and 18 months and by 25% between 18 and 36 months. This is comparable to the reduction of radiologically confirmed pneumonia in randomized controlled trials, and to the post licensure findings from the United Kingdom. However, the definition of LRTIs used in the current study lacks diagnostic specificity. Keeping in mind that the efficacy of PCV7 immunization in randomized controlled trials increase with disease severity, the reduction of LRTIs observed in the present study is high. This may be due to the rapid and high uptake of PCV7 immunization in Norway, or possibly due to a protective effect against viral pneumonias and bacterial co-infections, as proposed by a South African trial¹⁵.

The results of the present study may indicate that the overall impact of PCV7 immunization is higher when included in a childhood immunization program compared with clinical trials. This may reflect the influence of both direct and indirect vaccine effects. The direct and indirect vaccine effects contribute synergistically to the population-wide impact observed in post licensure studies. Since 99.1% of non-immunized children in the present study were born before 2006, this left a very small comparison group after PCV7 was introduced, and the current study was therefore not able to distinguish between a direct and indirect vaccine effect. Furthermore, observed reductions in respiratory tract infections after introduction of PCV7 immunization varies between countries, which might be due to differences in the immunization schedules, the rate of vaccine uptake, and may also be influenced by secular trends.

It is important to keep in mind that the reduction in the incidence of the respiratory tract infections examined by year of birth and immunization status, in addition to the differences in maternal and child characteristics by immunization status, may also reflect other secular trends than the introduction of PCV7, as well as changes in the geographic area of recruitment over the recruitment period into MoBa. An important secular change that has occurred over the study period is a substantial improvement of day care coverage after 2006, likely increasing the children's risk of respiratory tract infections^{31,32}. The prevalence of smoking has also decreased during the inclusion period into MoBa, which may have decreased the risk of respiratory tract infections^{33–36}. The current study controlled for both these factors. Immunization with the seasonal influenza vaccine of children younger than 36 months in Norway is only recommended for a few high risk groups, and should not have an impact on the associations examined. The time period included in the current study also includes the H1N1 epidemic in 2009. Approximately 50% of children younger than 36 months of age in Norway were vaccinated with the H1N1 vaccine in 2009, which may have had an influence on disease occurrence during the winter 2009/2010, but individual data on H1N1 immunization was not available for the current study. Influence of other secular trends cannot be ruled out.

The study has several limitations. The exact time of disease experience was not available, and the time from immunization to disease could not be measured. However, we used reports of disease occurring after immunization to reduce reverse associations. Using maternal report of child respiratory disorders may have resulted in misclassification, and the question asked to the mothers whether the child has experienced the respiratory disorders of interests likely includes diagnoses not confirmed by a doctor. However, questionnaires were consistent throughout the study, and a study comparing maternal report of child asthma at 7 years of age in MoBa to registered use of anti-asthmatic medications in the Norwegian Prescription Database found a strong agreement³⁷. A selection bias may also be present, as the children with the necessary follow up information at 18 and 36 months of age may constitute a distinct group of the cohort with regard to health awareness, disease occurrence or other factors that could have influenced the associations examined.

Population based surveillance of community-acquired respiratory tract infections, such as AOM and LRTIs, is difficult due to lack of diagnostic specificity and inconsistent use of health care services. The data from MoBa provides a unique opportunity to evaluate the impact of PCV7 immunization on the respiratory disorders examined. The large sample size, individual immunization status from SYSVAK, and the amount of maternal and child demographic information available from MoBa and MBRN strengthen the associations identified.

In conclusion, reduced incidences of AOM and LRTIs before 36 months of age were observed among children immunized with PCV7 through the childhood immunization program. In April 2011, the PCV7 was replaced by the 13-valent pneumococcal conjugate vaccine, and the public health impact of the increased serotype coverage and its possible influence on respiratory tract infections should be evaluated in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet*. 2009; 374:893–902. [PubMed: 19748398]
2. Drummond P, Clark J, Wheeler J, Galloway A, Freeman R, Cant A. Community acquired pneumonia--a prospective UK study. *Arch Dis Child*. 2000; 83:408–412. [PubMed: 11040149]
3. Michelow IC, Olsen K, Lozano J, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. *Pediatrics*. 2004; 113:701–707. [PubMed: 15060215]
4. Dagan R. The potential effect of widespread use of pneumococcal conjugate vaccines on the practice of pediatric otolaryngology: the case of acute otitis media. *Curr Opin Otolaryngol Head Neck Surg*. 2004; 12:488–494. [PubMed: 15548905]
5. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med*. 2001; 344:403–409. [PubMed: 11172176]

6. Destefano F, Pfeifer D, Nohynek H. Safety profile of pneumococcal conjugate vaccines: systematic review of pre- and post-licensure data. *Bull World Health Organ.* 2008; 86:373–380. [PubMed: 18545740]
7. Oosterhuis-Kafeja F, Beutels P, Van DP. Immunogenicity, efficacy, safety and effectiveness of pneumococcal conjugate vaccines (1998–2006). *Vaccine.* 2007; 25:2194–2212. [PubMed: 17267077]
8. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatr Infect Dis J.* 2000; 19:187–195. [PubMed: 10749457]
9. Theodoratou E, Johnson S, Jhass A, et al. The effect of Haemophilus influenzae type b and pneumococcal conjugate vaccines on childhood pneumonia incidence, severe morbidity and mortality. *Int J Epidemiol.* 2010; 39(Suppl 1):i172–i185. [PubMed: 20348119]
10. Cutts FT, Zaman SM, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet.* 2005; 365:1139–1146. [PubMed: 15794968]
11. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med.* 2003; 349:1341–1348. [PubMed: 14523142]
12. O'Brien KL, Moulton LH, Reid R, et al. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. *Lancet.* 2003; 362:355–361. [PubMed: 12907008]
13. Black SB, Shinefield HR, Ling S, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. *Pediatr Infect Dis J.* 2002; 21:810–815. [PubMed: 12352800]
14. Hansen J, Black S, Shinefield H, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than 5 years of age for prevention of pneumonia: updated analysis using World Health Organization standardized interpretation of chest radiographs. *Pediatr Infect Dis J.* 2006; 25:779–781. [PubMed: 16940833]
15. Madhi SA, Klugman KP. A role for Streptococcus pneumoniae in virus-associated pneumonia. *Nat Med.* 2004; 10:811–813. [PubMed: 15247911]
16. 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; 37:1155–1164. [PubMed: 14557958]
17. 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; 20:951–958. [PubMed: 11642629]
18. Dagan R, Givon-Lavi N, Zamir O, Fraser D. Effect of a nonavalent conjugate vaccine on carriage of antibiotic-resistant Streptococcus pneumoniae in day-care centers. *Pediatr Infect Dis J.* 2003; 22:532–540. [PubMed: 12799510]
19. 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; 22:10–16. [PubMed: 12544402]
20. Thorburn AN, O'Sullivan BJ, Thomas R, et al. Pneumococcal conjugate vaccine-induced regulatory T cells suppress the development of allergic airways disease. *Thorax.* 2010; 65:1053–1060. [PubMed: 20965927]
21. Grijalva CG, Poehling KA, Nuorti JP, et al. National impact of universal childhood immunization with pneumococcal conjugate vaccine on outpatient medical care visits in the United States. *Pediatrics.* 2006; 118:865–873. [PubMed: 16950975]
22. Grijalva CG, Nuorti JP, Arbogast PG, Martin SW, Edwards KM, Griffin MR. Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. *Lancet.* 2007; 369:1179–1186. [PubMed: 17416262]
23. Koshy E, Murray J, Bottle A, Sharland M, Saxena S. Impact of the seven-valent pneumococcal conjugate vaccination (PCV7) programme on childhood hospital admissions for bacterial

- pneumonia and empyema in England: national time-trends study, 1997–2008. *Thorax*. 2010; 65:770–774. [PubMed: 20805169]
24. Poehling KA, Szilagyi PG, Grijalva CG, et al. Reduction of frequent otitis media and pressure-equalizing tube insertions in children after introduction of pneumococcal conjugate vaccine. *Pediatrics*. 2007; 119:707–715. [PubMed: 17403841]
 25. Wals PD, Carbon M, Sevin E, Deceuninck G, Ouakki M. Reduced physician claims for otitis media after implementation of pneumococcal conjugate vaccine program in the province of Quebec, Canada. *Pediatr Infect Dis J*. 2009; 28:e271–e275. [PubMed: 19710582]
 26. Vestrheim DF, Lovoll O, Aaberge IS, et al. Effectiveness of a 2+1 dose schedule pneumococcal conjugate vaccination programme on invasive pneumococcal disease among children in Norway. *Vaccine*. 2008; 26:3277–3281. [PubMed: 18456376]
 27. Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C. Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol*. 2006; 35:1146–1150. [PubMed: 16926217]
 28. Nilsen RM, Vollset SE, Gjessing HK, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol*. 2009; 23:597–608. [PubMed: 19840297]
 29. Norwegian Public Health Institute. [Accessed September 15, 2011] The Norwegian Mother and Child Cohort Study Questionnaires. 2010. Available at: http://www.fhi.no/eway/default.aspx?pid=238&trg=MainArea_5811&MainArea_5811=5903:0:15,3138:1:0:0::0:01-9-0011.
 30. White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. *Stat Med*. 2010; 29:2920–2931. [PubMed: 20842622]
 31. Cote SM, Petitclerc A, Raynault MF, et al. Short- and long-term risk of infections as a function of group child care attendance: an 8-year population-based study. *Arch Pediatr Adolesc Med*. 2010; 164:1132–1137. [PubMed: 21135342]
 32. Kamper-Jorgensen M, Wohlfahrt J, Simonsen J, Gronbaek M, Benn CS. Population-based study of the impact of childcare attendance on hospitalizations for acute respiratory infections. *Pediatrics*. 2006; 118:1439–1446. [PubMed: 17015534]
 33. Alpert HR, Behm I, Connolly GN, Kabir Z. Smoke-free households with children and decreasing rates of paediatric clinical encounters for otitis media in the United States. *Tob Control*. 2011; 20:207–211. [PubMed: 21270071]
 34. Haberg SE, Bentdal YE, London SJ, Kvaerner KJ, Nystad W, Nafstad P. Prenatal and postnatal parental smoking and acute otitis media in early childhood. *Acta Paediatr*. 2010; 99:99–105. [PubMed: 19764924]
 35. Keskinoglu P, Cimrin D, Aksakoglu G. The impact of passive smoking on the development of lower respiratory tract infections in children. *J Trop Pediatr*. 2007; 53:319–324. [PubMed: 17517813]
 36. Moore HC, de KN, Richmond P, Lehmann D. A retrospective population-based cohort study identifying target areas for prevention of acute lower respiratory infections in children. *BMC Public Health*. 2010; 10:757. [PubMed: 21138593]
 37. Furu K, Karlstad O, Skurtveit S, et al. High validity of mother-reported use of antiasthmatics among children: a comparison with a population-based prescription database. *J Clin Epidemiol*. 2011; 64:878–884. [PubMed: 21232920]