Vaccine 32 (2014) 6948–6955

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Maternal immunization with pneumococcal 9-valent conjugate vaccine and early infant otitis media☆

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ARTICLE INFO

Article history:
Received 5 August 2014
Received in revised form 13 October 2014
Accepted 20 October 2014
Available online 30 October 2014

Keywords:
Pneumococcus
Otitis media
Maternal immunization
Pneumococcal antibodies

ABSTRACT

A randomized trial of an investigational 9-valent pneumococcal conjugate vaccine (PCV-9) or placebo given to pregnant women during the last trimester to prevent early infant otitis media (OM) was conducted. All infants received Prevnar® at 2, 4, 6, and 12 months. Clinic and adverse event records were reviewed to identify OM. Variables significantly related to acute OM by age 6 months ($p < 0.05$) were: vaccine group (9 valent or placebo), sibling history of tympanostomy tubes, upper respiratory infection, and number of clinic visits by 6 months. Infant OM rates were similar between 6 and 12 months (58% and 56%). Results suggested that immunizing pregnant women with PCV-9 increased infants' risk of acute OM in the first 6 months of life, and this correlated with decreased infant antibody responses to their infant *Streptococcus pneumoniae* vaccine serotypes, but did not influence antibody responses to 3 other serotypes two of which were in maternal vaccine (types 1 and 5) and one was a control (type 7F). Explanations for these results include dampening of infant antibody production by high levels of passively acquired maternal pneumococcal antibodies and/or altered B lymphocyte immune responses in infants exposed to these specific polysaccharide antigens in utero.

1. Introduction

Since the 1990s, obstetricians and pediatricians have advocated for maternal immunization during pregnancy to prevent neonatal morbidity and mortality [1–3]. The rationale for their position is that infants are immunologically immature, and typically do not produce protective antibody levels until after the primary vaccine series is given in the first 6 months of life. A cohort study conducted in the 1990s showed that infant cord blood IgG levels to *Streptococcus pneumoniae* (*S. pneumoniae*) types 14 and 19F in the lowest quartile predicted acute otitis media (AOM) onset in the first 6 months of life [4]. Others have shown that AOM onset in the first 6 months of life predicts recurrent AOM and chronic otitis media with effusion (OME) [5,6].

Randomized trials have demonstrated that heptavalent pneumococcal conjugate vaccine (PCV-7) is moderately efficacious in preventing AOM and recurrent AOM in infants and children, especially episodes caused by *S. pneumoniae* vaccine serotypes and cross-reacting serotypes [7–9]. Reductions of −1% to 7% in AOM and 9% to 16% in recurrent AOM were demonstrated in these trials. Prior to routine infant immunization with PCV-7, *S. pneumoniae* was the most prevalent bacterium cultured from the middle ear in children with AOM and persistent AOM [10–12]; 40% of middle ear pneumococcal isolates were antibiotic resistant [13].

The Maternal Infant Vaccine Study (MIVS), a Phase I/II randomized, double-masked trial of maternal immunization with an investigational 9-valent pneumococcal conjugate vaccine, diluted in aluminum phosphate (PNCRM9), hereafter referred to as PCV-9, [Wyeth Lederle] at 30–35 weeks of pregnancy, was designed to determine safety and maternal and infant antibody response [14]. The aim of the current study was to determine whether maternal immunization during pregnancy would prevent AOM onset in early

☆ The trial is registered at ClinicalTrials.gov, number NCT00617682.

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http://dx.doi.org/10.1016/j.vaccine.2014.10.060
0264-410X/

infancy. We hypothesized that since maternal antibodies cross the placenta, infants of mothers immunized in late pregnancy would have higher levels of pneumococcal antibody at birth and thus fewer AOM episodes in early life. Data to explore this aim were collected during the MIVS study and were analyzed. Secondary aims included (1) AOM and otitis media (OM) incidence from birth to 12 months and from 6 to 12 months by randomized maternal treatment group, and (2) predictors for OM in these two time periods.

2. Materials and methods

2.1. Patient enrollment

Research nurses recruited and enrolled pregnant women between November 2000 and March 2003 from seven HealthPartners clinics, an integrated health care system in the Minneapolis-St. Paul metropolitan area serving both urban and suburban residents. Women were recruited by letter, telephone, and personal contact at each clinic beginning at 20 weeks of pregnancy. Eligibility of interested women was determined by interview and medical record review. They were excluded from the study if they had prior immunization with pneumococcal vaccine, were at risk for preterm delivery, or had a condition that would be compromised by immunization. Protocol and consent forms were reviewed and approved by the Institutional Review Boards of the University of Minnesota, HealthPartners and the community hospitals where study infants were delivered. An External Data Safety and Monitoring Board was appointed (see Acknowledgements for members). Consent was obtained from both parents unless the father was unavailable. To assure similar size treatment groups at each clinic, participants were block randomized within clinic to receive PCV-9 or saline placebo. The vaccine lot number was #7-5021-013A. At the 30–35 week prenatal visit, a research nurse reconfirmed eligibility of the participant and administered a single 0.5 mL dose (saline placebo or PCV-9) injection into the deltoid with a 23 gauge 1 in. sterile needle. Investigators, research nurses, physicians, study staff and participants were all masked to product identity and randomization group.

2.2. Patient monitoring

Nurses contacted participants by phone 1–3, 4–7 and 8–14 days after immunization to gather information about local and systemic reactions and adverse events (AE), and at 34–36 and 38–40 weeks of pregnancy to determine changes in health status. Maternal AEs were monitored from immunization to delivery, infant AEs were monitored from maternal immunization until 13 months of age. Information for both mothers and infants was obtained by phone interview, maternal diary, and from medical records.

Mothers were interviewed by phone between 28 and 35 weeks gestation to gather data about demographic factors, family OM history, maternal smoking and alcohol consumption. Additional risk factor data (parental smoking, breastfeeding, daycare attendance and exposure to other children) were collected at 2 and 6 months of age by phone contact. Maternal interviews were conducted every 2 months to ascertain interim infant illnesses and visits to health care providers within and outside of HealthPartners. At the 6 month visit, mothers were asked which product they thought they had received (vaccine or placebo). Rates of infant follow-up were 99% in the first 6 months, and 80% from 6 to 12 months. Infants were seen an average of once a month in both groups during the first 6 months.

Infants received Prevnar®, PCV-7, at 2, 4, 6, and 12 months of age.

2.3. Abstraction of episodes of otitis media and other respiratory illness

HealthPartners abstractors recorded data from all clinic visits entered in the HealthPartners medical record. When a mother or infant was seen outside the HealthPartners system, a medical record release form was signed for that facility, and data from those visits were obtained and abstracted by the University of Minnesota coordinator. Data on type of visit (ill, recheck, well child); symptoms (fever, ear pain, irritable/fussy, not sleeping, difficulty hearing, not eating/eating poorly), ear exam findings (abnormal tympanic membrane position, color, appearance, mobility, perforation; presence and type of middle ear effusion); and middle ear diagnosis (normal, acute [suppurative] OM, serous OM, other OM) were also recorded through 13 months of age. An ear exam form, in use for years with other OM studies, was used in this study by the physicians.

These ear exam forms were scanned into a database. The study coordinator reviewed the database and ran queries to identify and remediate inconsistent entries (e.g. tympanic membrane recorded as not visualized, but ear exam findings present) and other data discrepancies. The coordinator also reviewed interim illness and adverse event data collected every two months by research nurse interview to identify visits outside the HealthPartners system. The medical records obtained for these visits were subsequently abstracted and added to the database.

After identifying discrepancies, the coordinator compared ear exam data against the medical record to resolve data entry, scanning and abstractor errors. Changes and corrections were recorded on Data Resolution Forms, and entered into the database. Physician diagnosis of middle ear status was used unless it was inconsistent with middle ear findings (e.g. air-effusion level, normal diagnosis). For infants with inconsistent findings, Drs. Ferrieri and Daly reviewed ear exam findings, physicians' dictation, recorded signs and symptoms, adverse event log, and diagnosis code to determine a middle ear diagnosis code for the child using the preponderance of evidence. They were blinded to maternal vaccine vs. placebo status. Nearly all discrepancies between ICD-9 code and diagnosis were reconciled after review of the medical record. If ears had different findings (i.e. right ear serous, left ear AOM), suppurative OM rather than non-suppurative OM was used for the child's diagnosis. The term OM includes all otitis media diagnoses, while AOM referred specifically to suppurative OM diagnoses.

Upper respiratory infection (URI) was determined as follows: (1) URI was diagnosed and an ICD-9 code was recorded by a physician, or (2) the term URI (or cold) was mentioned in physician dictation or other documentation (AE log, symptom diary, illness interviews), but not coded, or (3) URI was not recorded with a code, but determined from documented signs and symptoms indicative of URI.

2.4. Blood draws and antibody assay

Cord blood samples were drawn at delivery, and maternal samples were drawn prior to immunization, at delivery, and at 2, 6, and 13 months post-immunization. Infant blood samples were drawn at 6, 7, 12 and 13 months. Type-specific pneumococcal antibody assays were performed on all sera.

Type-specific pneumococcal antibody titers were measured to nine vaccine serotypes (1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F) and control serotype 7F. IgG antibodies against pneumococcal capsular polysaccharides (PS) were analyzed by enzyme-linked immunosorbant assay (ELISA) using Costar 96-well microtiter plates (Corning Incorporated, Corning, NY) for pneumococcal anti-PS IgG antibody against the national reference serum 89-SF (FDA/CBER, Bethesda, MD) using a modified World Health