Comparative Effectiveness of the 7-Valent Pneumococcal Conjugate Vaccine and Haemophilus Influenzae Type b Vaccine for the Prevention of Acute Otitis Media with Tympanic Membrane Perforation: A Secondary Analysis of Data from a Randomized Trial among Bangladeshi Infants

By

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ABSTRACT

Background:  Streptococcus pneumoniae is the most common bacterial cause of acute otitis media (AOM).  A few randomized controlled trials (RCTs) have found that administration of the pneumococcal conjugate vaccine (PCV) to infants is effective at decreasing episodes of AOM during infancy and early childhood.  However, these RCTs were in high-income countries in populations with a relatively low burden of suffering due to otitis media.  This trial is the first to use data from a randomized trial to investigate the effectiveness of a PCV at decreasing otitis media in a country with a high level of morbidity and mortality due to otitis media.

Methods: The effects of the 7-valent PCV and Haemophilus influenzae type b (Hib) conjugate vaccine on AOM with TM perforation were compared through a secondary analysis of data that were collected during a blinded, randomized trial in Bangladesh in 2004 and 2005.  Infants received vaccines at 6, 10, and 14 weeks of age and their caregivers were interviewed weekly from 6-24 weeks of age.  Caregiver report of ear drainage was considered to represent AOM with TM perforation.  Weekly interviews also asked about antibiotic use and other illness symptoms.

Results:  340 infants were enrolled and randomized.  Data were collected and analyzed for 328 infants.  Baseline data were comparable between the two groups.  In the PCV and Hib vaccine groups there were similar numbers of episodes of AOM with TM perforation and similar numbers of infants who had one or more episodes.  However, in the PCV group there were fewer positive weekly reports of AOM with TM perforation total.  Infants in the PCV group had an average of 1.2 weekly reports per episode, compared to those in the Hib vaccine group who had an average of 2.6 weekly reports per episode (p = 0.005).  In the PCV group antibiotics were given during the first week of an episode of AOM with TM perforation in 82% of weeks compared to only 25% of such weeks in the Hib vaccine group (risk difference: 57%, 95% C.I. 23% – 90%).  A multivariate analysis that accounted for the type of vaccine and for antibiotics given during the first week of an episode found that neither had a statistically significant effect on the number of weekly reports per episode of AOM with TM perforation (p= 0.10 for vaccine type, p= 0.33 for antibiotics).

Conclusions:  The results suggest that the 7-valent PCV does not cause a statistically significant difference in the incidence or duration of episodes of AOM with TM perforation among infants in Bangladesh.  However, due to significant concerns about the internal validity of the study, the accuracy of these results is unclear and they should be interpreted with caution.  The potential for measurement errors, the use of the Hib vaccine in the comparison group, and the poor adherence to the intervention constitute the greatest concerns about the internal validity of the study.  On March 21, 2015, Bangladesh added a 10-valent PCV to its national immunization program, creating the opportunity for the use of historical cohort studies to research this topic in the future.
INTRODUCTION

Streptococcus pneumoniae is a bacterial pathogen that is responsible for an estimated 1 million or 1.8% of all deaths* and 35 million or 1.4% of all disability-adjusted life-years (DALYs) worldwide every year.¹² Most of the morbidity and mortality due to S. pneumoniae is caused by pneumonia and meningitis, but otitis media, sinusitis, and bacteremia are significant contributors as well.³ S. pneumoniae is responsible for more deaths in children under 5 than any other single pathogen.⁴ It causes 8% of deaths in children under 5 years of age and 11% of deaths in children between 1 month and 5 years of age.⁵

Compared to other age groups, children under 5 are disproportionately affected by S. pneumoniae infections. Despite being only 9% of the population, children under 5 account for an estimated 22% of the deaths, 52% of the DALYs, and 54% of the years of life lost (YLLs) due to S. pneumoniae.¹²⁶ In addition to this age-related disparity, there are geographic and economic disparities in the burden of suffering due to S. pneumoniae in children under 5. Africa and Southeast Asia account for an estimated 77% of the all deaths due to S. pneumoniae in children under 5, even though they are home to 48% of the world’s children under 5.⁵ From an economic perspective, 61% of all deaths due to S. pneumoniae in children under 5 occur in only ten low and middle-income countries in Africa and Asia.⁵

Several strategies have been suggested for decreasing the large burden of suffering due to S. pneumoniae and for reducing the disproportionately high morbidity and mortality it causes among children under 5 in low and middle-income countries in Africa and Asia. Suggested

*There is substantial variation in estimates of deaths due to S. Pneumonia. The estimate above is for the year 2010 from the Global Burden of Disease project undertaken by the Institute for Health Metrics and Evaluation (IHME) associated with the University of Washington.¹² Another estimate by the IHME was significantly lower.⁴ An estimate generated by the World Health Organization (WHO), Pneumococcal vaccines Accelerated Development and Introduction Plan (PneumoADIP), and Global Alliance for Vaccines and Immunization (GAVI) was significantly higher.⁵
strategies include expanding pneumococcal conjugate vaccine (PCV) coverage, decreasing secondhand smoke exposure, improving nutrition, increasing breastfeeding, providing zinc supplementation, and boosting access to antibiotic treatment for bacterial pneumonia. This master’s paper investigates one of those strategies, the expansion of PCV coverage, which has been a significant focus of international efforts and research since 2000.

**Efficacy and Impact of the PCV**

A meta-analysis from 2009 examined seven randomized, controlled trials (RCTs) (total n = 111,798) and calculated the effects of the 7, 9, and 11-valent PCVs in children <29 months of age. It found that the PCV was effective at reducing invasive pneumococcal disease (IPD) (relative risk (RR): 0.42, 95% CI 0.27 – 0.65). One of the RCTs even found that the 9-valent PCV decreased all-cause mortality among children in Kenya (n = 17,437, RR: 0.86, 95% CI 0.77 – 0.98). Two of the RCTs found trends toward reductions in all-cause mortality among children in the Philippines with the 11-valent PCV (n = 12,191, RR: 0.88, 95% CI 0.5 – 1.5) and in South Africa with the 9-valent PCV (n = 37,259, RR: 0.95, 95% CI 0.8 – 1.1). When those results were pooled with a smaller study of the 7-valent PCV in Finland (n = 1,251, RR: 1.50 95% CI 0.1 – 36), the meta-analysis found that PCVs caused a relative reduction of 11% in all-cause mortality (n = 68,138, RR: 0.89, 95% CI 0.80 – 0.98).

The use of the PCV began in high-income countries in 2000, and its effects in those countries have been positive and well-documented. A non-systematic review described nine historical comparison studies that compared the incidence of IPD before and after the addition of the 7-valent PCV to the national immunization schedules of eight high-income countries. The studies found reductions of 37% – 80% in IPD due to all S. pneumoniae serotypes and reductions of 79% – 100% in IPD due to the 7 vaccine serotypes. Despite the substantial evidence that the
PCV is beneficial and efficacious at reducing morbidity and mortality, it is still only available and accessible to 49% of the world’s children.\textsuperscript{13}

**PCV Use in Lower and Middle-Income Countries**

As of 2008, the PCV was not included in the immunization schedules of any low or middle-income countries.\textsuperscript{3} However, PCV coverage has improved substantially in the last 7 years.\textsuperscript{13} One of the major organizations leading the effort to increase the number of children who receive the PCV is the Global Alliance for Vaccines and Immunizations (GAVI). Much of the expansion in PCV coverage has been through a GAVI program that offers significant financial and technical assistance to countries with a gross national income of less than $1,000 per person.\textsuperscript{3,11} Of the 73 GAVI-eligible countries, 53 currently provide PCV coverage through their national immunization programs and 12 others are in the process of adding PCV coverage.\textsuperscript{13} Among the ten countries with the most childhood deaths due to S. pneumoniae, seven have added the PCV to their immunization programs since 2011. In the three remaining countries, India, China, and Indonesia, the PCV is not a part of their immunization programs.\textsuperscript{10} Since these three countries account for 40% of the world’s population, it is not surprising that 51% (69 million) of infants worldwide live in countries where the PCV is not part of the national immunization program.\textsuperscript{13} Of these three countries, the burden of suffering due to S. pneumoniae is greatest in India, which has more childhood deaths due to S. pneumoniae than any other country. India accounts for about 17% of the world’s total, compared to 3.6% in China and less than 2.3% in Indonesia.\textsuperscript{5}

**Potential Relevance of the Analysis**

The analysis described in this master’s paper is relevant because it has the potential to provide additional evidence to support the expansion of PCV coverage, especially in India. It is
a secondary analysis of data from a randomized trial, and it investigates the effect of the 7-valent PCV on acute otitis media (AOM) with tympanic membrane (TM) perforation among infants in Bangladesh.* (See Appendix A for more about AOM with TM perforation and the other types of otitis media.) Although the existing evidence for the benefit of the PCV described above is already substantial, this analysis could add to it in two ways.

1) This analysis is the first to investigate the effect of the PCV in the WHO South-East Asia region, making it potentially the first study to demonstrate that the PCV is effective against the S. pneumoniae serotypes in that region.12,14 This is important because of the considerable geographic variation in S. pneumoniae serotypes, such that in Asia only about 50% of pneumococcal serotypes are covered by the 7-valent PCV, compared to 82% in North America and 72% in Europe.15 The Indian Academy of Pediatrics Committee on Immunization even expressed concerns about the implications of geographic variation of S. Pneumonia

* Eliza RoyA and Mark SteinhoffB,C came up with the original idea for this secondary analysis. I wrote a manuscript that carried out their original idea, with guidance and editing from Mark Steinhoff. That manuscript is separate from this master’s paper. This master’s paper is similar to that manuscript because it investigates the same hypothesis using the same data. However, there are several key differences, which are that the master’s paper has a different introduction, uses different terminology and outcome variables, adjusts for confounders in the statistical analysis, and has different interpretations of the results. The manuscript is in the process of being prepared for publication, and its most recent version is included as Appendix C of this master’s paper. The manuscript is entitled, “Clinical Effectiveness of a Pneumococcal Conjugate Vaccine in Acute Suppurative Otitis Media: A Randomized Controlled Trial in Bangladeshi Infants.” The analysis described in the manuscript was approved by the Cincinnati Children’s Hospital Medical Center Institutional Review Board. The other authors listed for the manuscript are S.B. OmerD, S.E. ArifeenA, R. RaqibA, R.F. BreimanE, and K. Zaman.A They were all involved in the design and implementation of the initial Mother’s Gift trial and had peripheral involvement in the manuscript. Statistical analysis for the manuscript was performed by Caitlin Dodd.C The results for the primary outcomes from the Mother’s Gift trial have not been published yet. Several articles describing the results of other secondary analyses of the Mother’s Gift trial data have been published, and they are included in the reference list.16-25

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serotypes in its 2012 immunization recommendations. Since the demographic, geographic, and population health characteristics of Bangladesh and India are very similar, if this analysis finds that the 7-valent PCV significantly decreases AOM with TM perforation among infants in Bangladesh, then that finding would be reasonably generalizable to India. Since S. pneumoniae causes about 25–62% of AOM, finding that the PCV substantially decreases AOM with TM perforation could suggest that the PCV is effective against an adequate number of S. pneumoniae serotypes in the region. That evidence could potentially help convince policy makers in India to add the PCV to its Universal Immunization Program (UIP).

2) This analysis is also the first to use data from a randomized trial to investigate the effect of the PCV on otitis media in a country with a high burden of suffering due to otitis media. Both Bangladesh and India certainly meet this criterion. Otitis media causes an estimated 3,500 deaths and 4.7 million DALYs worldwide every year. A substantial portion of those occur in the South Asia WHO subregion, which is composed of Afghanistan, Bangladesh, Bhutan, India, Nepal, and Pakistan. The South Asia subregion has 23% of the world’s population, but it accounted for an estimated 48% of the deaths due to otitis media in 2005. The subregion also accounted for astounding proportions of the hearing impairment (HI) caused by otitis media, which were an estimated 75% of the moderate HI, 85% of the severe HI, and 93% of the profound HI due to otitis media. Much of this burden of suffering due to otitis media in South Asia likely comes from India, since it has 75% of the subregion’s population. (See Appendix B, for more information about the burden of suffering due to otitis media.)

Three previous RCTs investigated the effect of PCV administration to infants on otitis media, and they found relative risk reductions of 6–34% in the incidence of AOM. However, those studies were in high-income countries that have a much lower incidence and
prevalence of otitis media.\textsuperscript{29,36} If this analysis finds that the PCV decreases AOM with TM perforation among infants in Bangladesh, it would provide new evidence that the PCV might prevent substantial morbidity and mortality in India by decreasing deaths, hearing impairment, and other complications due to otitis media. That potential finding, in combination with the existing evidence that the PCV decreases IPD in children, might also help convince policy makers to add the PCV to India’s UIP.

\textbf{METHODS}

\textbf{Study Design}

This study compares the effects of the PCV and Haemophilus influenzae type b (Hib) conjugate vaccine on AOM with TM perforation in infants. It is a randomized, comparison-controlled, parallel group study, involving the secondary analysis of data that were originally collected in Bangladesh in 2004 and 2005 for the Mother’s Gift trial. Although the data for this analysis were collected prospectively, the outcomes it evaluates were chosen retrospectively. The Mother’s Gift trial collected a large amount of interview data to monitor for possible adverse effects. The decision to pursue this secondary analysis was made after a post-hoc examination of the interview data uncovered a significant difference in the reports of AOM with TM perforation between infants who received the PCV and Hib vaccine. The protocol for this secondary analysis was evaluated by the institutional review board (IRB) at the University of North Carolina at Chapel Hill, which judged that it did not require formal IRB approval because it used de-identified data that contained no identifiable private information.

This analysis is comparison-controlled and uses the Hib vaccine as the comparator, so it is not a placebo-controlled study. However, the consideration of the analysis’ potential relevance in the introduction and the interpretation of the results in the discussion generally
regard the Hib vaccine as a quasi-placebo because its effect on otitis media is very small.\textsuperscript{28,37}
The rationale for this is further explained in the discussion section on pages 22-23 below, in the subsection entitled “Limitations due to Study Design.”

**Data Source**

The Mother’s Gift trial (ClinicalTrials.gov number NCT00142389), investigated whether the immunization of pregnant women with the pneumococcal polysaccharide vaccine (PPV) might decrease the immunogenicity of the PCV among their infants or cause other adverse effects. Its primary and secondary outcomes were adverse reactions to the vaccines and infants’ levels of anti-pneumococcal immunoglobulin G (IgG) antibodies at 20 weeks and 12 months of age.\textsuperscript{38} The results of the pre-specified primary and secondary outcomes from the Mother’s Gift trial have not yet been published. Several articles describing analyses of Mother’s Gift trial data have been published, and they are included in the reference list.\textsuperscript{16-25} The Mother’s Gift trial investigated whether maternal PPV immunization interferes with the immunogenicity of the PCV among infants or causes other significant negative adverse effects. If the trial finds that maternal PPV immunization does neither of those things, then its authors have planned to perform a larger study to investigate the effect of maternal PPV immunization on IPD in infants (especially during the first several weeks of life before infants receive their initial doses of the PCV).

The Mother’s Gift trial protocol was reviewed and approved by the IRBs at the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B) and the Bloomberg School of Public Health at Johns Hopkins University. Monitoring for adverse events during the Mother’s Gift trial was conducted through the weekly interviews described below. An independent data and safety monitoring board and the two above IRBs reviewed all possible
severe adverse events. Use of study vaccines was approved by the Directorate of Drug Administration of the Government of the People's Republic of Bangladesh.

**Participants**

Maternal participants were recruited into the Mother’s Gift trial from three urban, antenatal clinics in Dhaka, Bangladesh. All women in their third trimester of pregnancy who attended one of the three antenatal clinics between August 2004 and May 2005 were screened for participation in the study. Inclusion criteria were women who were 18-40 years of age, had a normal medical and obstetric history, and planned to remain in Dhaka for one year after delivery. Exclusion criteria were the receipt of a pneumococcal vaccine in the previous 3 years, a contraindication to getting a study vaccine, a last menstrual period (LMP) date not consistent with the clinical examination, and a previous history of a systemic disease, pregnancy complication, preterm delivery, abortion, birth with a congenital anomaly, or allergic reaction to a vaccination.

Sample size calculations performed for the Mother’s Gift trial deemed that 336 mother-infant pairs would be necessary to detect a difference in the mean pneumococcal antibody titers of the infant participants (based on reported local antibody variance data, a 2-sided $\alpha = 0.05$, a $\beta = 0.20$, and an assumed 25% attrition rate). No sample size calculations were performed for this secondary analysis.

**Interventions and Randomization**

Upon enrollment in the Mother’s Gift trial, the pregnant women were randomly assigned to receive either the PPV (23-valent, Pneumovax®, Merck) or the inactivated influenza vaccine (Fluarix®, GlaxoSmithKline). At that time, their future infants were assigned to receive either the PCV (7-valent, Prevnar®, Wyeth) or the Hib conjugate vaccine (PRP-T, Hiberix®,}
GlaxoSmithKline). For this analysis, the infants were divided based on the vaccine they received into the PCV group and the Hib vaccine group. Randomization was blocked to achieve similar numbers of each of the four possible maternal-infant vaccine combinations (Table 1). As a result, in both the PCV group and the Hib vaccine group, approximately half of the infants had mothers who received the PPV, and approximately half had mothers who received the influenza vaccine (Figure 1). Of note, the comparison vaccines (influenza and Hib) were included in the original Mother’s Gift trial because the ICDDR,B IRB would not approve a placebo-controlled trial and required that all participants receive the benefit of some type of vaccine in exchange for their participation in the trial.

Randomization was performed using a computer-generated sequence that was developed centrally before study enrollment began. Randomization was stratified by the three antenatal clinics. Sequentially-numbered, opaque envelopes with the vaccine assignments were provided to each clinic. Clinic staff who administered the vaccines were aware of the vaccine and group assignments, but they were not involved with the measurement of study outcomes. Other clinic staff, the participants and their families, and the study staff who collected the data were blinded to vaccine and group assignments.

Pregnant women received one dose of their assigned vaccine (PPV or influenza vaccine) during the third trimester of pregnancy. Infants were assigned to receive three doses of their study vaccine (PCV or Hib vaccine) at 6, 10, and 14 weeks of age. All vaccine doses were administered through intramuscular injection. All study vaccines were purchased from the manufacturers.

**Outcomes and Measurement**
The outcome data in this analysis were collected during weekly interviews with infants’ mothers (or other knowledgeable caregivers) between 6 and 24 weeks of age. According to the Mother’s Gift trial protocol, interviews were to occur every other week from birth to 6 weeks of age, then every week from 6 to 24 weeks of age. This analysis does not include data collected prior to 6 weeks of age because that was before any of the infants received the PCV or Hib vaccine. Although additional interviews occurred between 25 and 37 weeks of age, these interviews were excluded from the analysis because they were not performed consistently for all infants and because they were not part of the original trial protocol.

The weekly interviews included questions about infant feeding, illness symptoms, and treatments given to the infants. The questions most relevant to this analysis were those concerning respiratory and ear infections and antibiotic use. The interviewees were asked every week if the infant had had an ear problem during the last week. If the answer was yes, they were also asked if it involved drainage from one ear, both ears, or neither ear. The interviewees were also asked if the infant had had a respiratory illness during the last week. If the answer was yes, they were asked if it involved cough, runny nose, sore throat, difficulty breathing, and/or provider-diagnosed pneumonia. Whenever an ear problem or respiratory illness was reported, the interviewer asked if any treatments were given for the illness. The types of medications (antibiotic, antihistamine, antipyretic, etc.) were recorded, but the specific names of the medications were not recorded.

For this analysis, all reports of ear drainage were considered to represent purulent otorrhea due to AOM with TM perforation. The interview questions about ear problems and ear drainage did not differentiate between one day and seven days of symptoms during the last week. Nevertheless, this analysis assumes that consecutive weekly reports of ear drainage are assumed
to be all part of one episode, as opposed to two separate episodes with complete resolution in between. This is a reasonable assumption given the nature and clinical course of most ear infections and given that ear drainage that seems to resolve and then recur within a week is much more likely to be related to the initial AOM with TM perforation episode than to a new episode. This analysis did not attempt to calculate durations for episodes in days or weeks because of the imprecision inherent in the way the data were collected. Here are 3 examples that illustrate this concept. 1) If an infant had a 6 day episode of ear drainage that all occurred within one interview week, then that infant’s 6 day episode would have one positive weekly report. 2) If an infant had a 2 day episode of ear drainage, of which 1 day occurred during one interview week and 1 day occurred during the next, then that infant’s 2 day episode would have 2 positive weekly reports. 3) If an infant had a 12 day episode of ear drainage, of which 6 days occurred during one interview week and 6 days occurred during the next, then that infant’s 12 day episode would have 2 positive weekly reports. As a result of this imprecision, this analysis does not calculate the duration of episodes. Instead episodes are compared by their number of weekly reports, which preserves the vagueness of the data and most closely represents how the data were collected.

For weeks when infants had positive reports of AOM with TM perforation, they were considered to have received antibiotics for that infection if they were given an antibiotic intended to treat the AOM with TM perforation or an antibiotic intended to treat a respiratory illness. This is reasonable because the same antibiotics are generally prescribed for both respiratory and ear infections, since the bacteria that commonly cause both types infections in children are largely the same.
The weekly interviews were conducted by field workers, who were trained and overseen by study supervisors. The interviews were performed over the telephone, at an infant’s home, or at one of the study clinics. Weekly interviews at homes or in clinics included weight, height and mid-upper arm circumference (MUAC) measurements. Maternal height, weight, and MUAC were measured at the time of delivery. Maternal participants were interviewed about their baseline health and demographic characteristics soon after their enrollment in the study. They were interviewed about their deliveries within one week of their occurrence in almost all cases. Data on the number of vaccines received by infants were recorded in the clinics where the vaccines were given. Those data were not available for this analysis, but the weekly interviews included caregiver reports of vaccine administration, so those data were used instead.

**Statistical Analysis**

Baseline characteristics were measured for each group. Means or percentages were calculated as appropriate for each characteristic. Outcomes were reported as percentages and frequencies, and their statistical significance was determined by calculating the confidence intervals for the risk differences using standard formulae. Possible confounders were evaluated using the same approach. The average number of weekly reports per episode of AOM with TM perforation for each vaccine group were compared using the Wilcoxon rank-sum test performed using Stata® 12 software. Antibiotic treatment during the first week of an episode was identified as a possible confounder. The combined influence of vaccine group and antibiotic treatment on the number of weekly reports per episode was evaluated using the generalized linear model procedure in SAS® 9.4 software.

**RESULTS**

**Participants**
823 pregnant women were screened for study eligibility. 340 of them were enrolled in the study and randomized along with their future infants. The reasons why women did not enroll in the study are listed in Figure 2. After enrollment, but prior to the intervention of interest in this analysis, 12 infant participants (6 from each group) left the study. No outcome data were collected for these infants. Their data were not included in Table 2, which compared baseline participant characteristics. Figure 2 lists the reasons they left the trial, if they are known. Due to the departure of these 12 infants, there were 328 infants still in the trial when the infant vaccine portion of the intervention began. 165 of the remaining infants were in the PCV group, and 163 were in the Hib vaccine group.

Baseline health, biometric, and demographic characteristics of these 328 infants and their mothers are listed in Table 2. For most characteristics the differences between the PCV and Hib vaccine groups were small. For three characteristics there was a relative difference of >15% between the two groups. These were gestational age of <38 weeks, birth by cesarean section, and secondhand smoke exposure in the home. Each of these characteristics was more frequent in the PCV group, with absolute differences of 4.1%, 14%, and 6.2% respectively. Tests for statistical significance for these differences were not performed.

**Intervention**

Although the infant participants were all supposed to receive three doses of their assigned vaccine, it seems that only 9% in the PCV group and 7% in the Hib vaccine group received exactly three doses. The numbers of infants in each group receiving 0, 1, 2, 3, and 4 doses of their assigned vaccine are listed in Figure 2. As is noted above, these data are from caregiver reports during the weekly interviews and not from the clinic records, which were not available for this analysis.
Data Collection

According to the Mother’s Gift protocol, interviews about the infants’ health were to occur weekly between 6 and 24 weeks of age. Only 1.8% (3/165) of infants in the PCV group and 3.1% (5/163) in the Hib vaccine group were lost to follow up during data collection. After adjusting for the interviews missed due to these 8 infants that were lost to follow up, the expected number of weekly interviews was 3,114 for the PCV group and 3,048 for the Hib group. Interview data were collected for 99% of these expected weeks for both the PCV group (3,086/3,114) and the Hib vaccine group (3,020/3,048). Even though there was a high level of data completeness in both groups, not all of the data were collected on time. When one or more interviews did not occur during the assigned week, data for multiple weeks were often collected at the next interview. 2.3% (71/3,086) of PCV group interviews and 2.9% (87/3,020) of Hib vaccine group interviews were conducted at least one week late. The degree of lateness per group is further specified in Table 3. No weekly reports of AOM with TM perforation are from interviews that were ≥1 week late.

Interviews occurred in three different settings. Altogether, 47% of the weekly interviews were performed over the telephone, 43% were performed at infants’ homes, and 10% were performed at one of the study clinics. Table 4 lists the number of interviews for each type by vaccine groups, and it also lists the positive weekly reports of AOM with TM perforation for each interview type by group.

Even though the weekly interviews were supposed to end at 24 weeks of age, about two thirds of infants in both groups had at least one interview after 24 weeks. However, there were considerably fewer interviews for each week after 24 weeks of age, such that only 7% of infants had interviews after 28 weeks. The numbers of interviews after 24 weeks were similar for each
group with 246 for the PCV group and 281 for the Hib vaccine group. Investigators from the original trial believe that the weekly interviews may have continued for some participants beyond 24 weeks of age due to requests by the families. Three weekly reports of AOM with TM perforation occurred after 24 weeks, and they were not included in the data analysis. All three were in the Hib vaccine group. One report was on week 25 in an infant who had not had any prior reports of ear issues. The other two reports were on weeks 25 and 26 in an infant who had previous positive reports on weeks 15-19, 23, and 24 (Row 8 of Hib vaccine group in Figure 3).

Interview data prior to 6 weeks of age were excluded from the analysis because none of the infants received a study vaccine prior to 6 weeks of age. There were no weekly reports of AOM with TM perforation prior to 6 weeks.

**Outcomes**

In the PCV group, there were 13 positive weekly reports of AOM with TM perforation among the 165 infants, who had a total of 3,086 weekly interviews. The 13 weekly reports come from 9 infants who had a total of 11 episodes. In the Hib vaccine group, there were 31 positive weekly reports of AOM with TM perforation among the 163 infants, who had a total of 3,020 weekly interviews. The 31 weekly reports come from 10 infants who had a total of 12 episodes. These data are listed in Table 5 and depicted visually in Figure 3 by vaccine group, week, and infant.

The percentage of weeks with positive reports of AOM with TM perforation was 0.4% for the PCV group and 1.0% for the Hib vaccine group; the risk difference of 0.6% between the groups was statistically significant (95% C.I. 0.2% – 1.0%, Table 5). However, the percentage of infants with one or more weekly reports of AOM with TM perforation was similar for both groups at 5.4% in the PCV group and 6.1% in the Hib vaccine group, with a risk difference of
0.7%, which was not statistically significant (95% C.I. -6% – 4%, Table 5). The percentages of weekly interviews with a new episode were also similar for both groups at 0.36% for the PCV group and 0.40% for the Hib vaccine group, with a risk difference of 0.04%, which was not statistically significant (95% C.I. -0.3% – 0.3%, Table 5).

Review of the characteristics of the 19 infants with ≥1 episode of AOM with TM perforation revealed that 16 male infants had an episode of AOM with TM perforation compared to only 3 female infants (RR = 3.9, 95% C.I. 1.2 – 13). This sex difference was similar in both groups and is further detailed in Table 6. In the PCV group there were 8 males and 1 female with AOM with TM perforation. In the Hib vaccine group there were 8 males and 2 females with AOM with TM perforation.

There were similar numbers of episodes of AOM with TM perforation per group, but the total number of weekly reports was significantly higher in the Hib vaccine group, giving it more weekly reports per episode. Table 7 shows the average number of weekly reports of AOM with TM perforation per episode, which was 1.2 for the PCV group and 2.6 for the Hib vaccine group. For both groups the number of weekly reports per episode does not have a normal distribution due to substantial positive skew. As a result, the Wilcoxon rank-sum test was used and it found a statistically significant difference with a p value of 0.005. The median number of reports per episode and the \( z \) statistic value are also reported in Table 7.

The finding of similar numbers of episodes in both vaccine groups suggests that the PCV does not prevent episodes of AOM with TM perforation when compared to the Hib vaccine. However, the statistically significant difference in the number of weekly reports per episode suggests the possibility that PCV might decrease the duration of episodes of AOM with TM perforation compared to the Hib vaccine. In this analysis there were 23 episodes per 328 infants,
which is one episode per 14.3 infants. The findings above suggest that immunizing 14.3 infants with the PCV (compared to with the Hib vaccine) might not prevent any episodes of AOM with TM perforation between 6 and 24 weeks of age, but it might decrease the length of one episode during that time from about 2.6 weeks to 1.2 weeks.

**Possible Confounding Variables**

The data in this study are from an RCT, which appears to have had a large enough sample for effective randomization based on the results in Table 2. However, there were only 19 infants who had an episode of AOM with TM perforation, which is much smaller than the 328 infants whose data were considered in the full analysis. Consideration of possible confounders is appropriate in any secondary analysis of data from an RCT, but it is essential in this analysis since the statistically significant finding comes from such a small subset of the study sample.

Of the variables and characteristics measured in the original analysis, the two that are most likely to lead to an increased risk of longer episodes of AOM with TM perforation are exposure to secondhand smoke and antibiotic treatment.⁴²,⁴³ Among the infants with one or more weekly reports of AOM with TM perforation, 44% in the PCV group and 50% in the Hib vaccine group were exposed to secondhand smoke at home, for which the risk difference of 6% was not statistically significant (95% C.I. -39% – 50%, Table 8). Similarly, the percentage of episodes occurring among infants with secondhand smoke exposure was 46% in the PCV group and 55% in the Hib vaccine group, for which the risk difference of 9% was not statistically significant (95% C.I. -24% – 41%, Table 8). Given that the difference in secondhand smoke exposure between the two groups lacked statistical significance and was small in magnitude, it was not considered further as a possible confounder.
Among the infants with one or more weekly reports of AOM with TM perforation, there were considerable differences in antibiotic treatment between the two groups. The percentage of weeks when both AOM with TM perforation and antibiotic treatment were both reported was 85% in the PCV group and 52% in the Hib vaccine group, for which the risk difference of 33% was statistically significant (95% C.I. 7% – 59%, Table 9). Similarly the percentage of episodes of AOM with TM perforation when antibiotic treatment was reported during the first week of the episode was 82% in the PCV group and only 25% in the Hib vaccine group, for which the risk difference of 57% was statistically significant (95% C.I. 23% – 90%, Table 9). These results established that despite randomization antibiotic treatment was substantially and significantly different among the infants with episodes of AOM with TM perforation in the two groups. In general, antibiotic treatment is much more effective at decreasing the duration of AOM with TM perforation when it begins at the earlier stages of the infection. In addition, it is difficult to compare and analyze antibiotic treatment during different weeks of an episode in a way that is meaningful both clinically and statistically. As a result, further investigation into antibiotic use as a confounder focused on the effect of treating or not treating with antibiotics during the first week of episodes of AOM with TM perforation. A multivariate analysis using a generalized linear model was used to investigate whether the differences in antibiotic treatment during the first week of episodes could account for the difference in the number of weekly reports per episode between the two groups.

The generalized linear model found that when the influence of both vaccine type and antibiotic treatment during the first week were considered, neither had a statistically significant effect on the number of weekly reports per episode of AOM with TM perforation. The estimate value for vaccine in Table 10 indicates that the model found an average of 1.1 more weekly
reports per episode among infants in the Hib vaccine group compared to those in the PCV group, but this was not statistically significant \( (t = 1.7, p = 0.10) \). The estimate value for antibiotic treatment in Table 10 indicates that the model found an average of 0.6 more weekly reports for episodes that were treated with antibiotics during the first week compared to those that were not, but this was also not statistically significant \( (t = 1.0, p = 0.33) \).

**Adverse Events**

Data regarding adverse events were collected through interviews that occurred about one week after each vaccine was administered. Additional adverse events were identified through appointments at the study clinics for illnesses and for check-ups. Those data were not available for this analysis. However, a previously published secondary analysis of the same data found that there were 18 infants who were hospitalized between 5 and 24 weeks for the following reasons: gastroenteritis (6), pneumonia (5), septicemia (5), and meningitis (2).\(^{16}\) That analysis was concerned with maternal vaccine groups, so it did not report which vaccines the hospitalized infants received.

**DISCUSSION**

**Main Findings**

Similar percentages of infants experienced episodes of AOM with TM perforation in both the PCV and Hib vaccine groups. The incidence of new episodes was also similar for both groups. These findings suggest that among Bangladeshi infants less than 24 weeks of age the PCV, when compared to the Hib vaccine, does not decrease the number of infants who get AOM with TM perforation. They also suggest that it does not decrease the number of episodes they experience. However, infants in the PCV group, compared to those in the Hib vaccine group, had less than half as many weekly reports per episode and less than half the rate of weekly
reports overall. Before adjusting for confounding, these differences were statistically and clinically significant, such that immunizing 14 infants with PCV might decrease the duration of one episode of AOM with TM perforation prior to 24 weeks of age from 2.6 weeks to 1.2 weeks. However, after adjusting for antibiotic use during the first week of episodes, the difference in weekly reports per episode was no longer statistically significant (p = 0.10).

A multivariate analysis using a generalized linear model calculated how vaccine type and antibiotic use during the first week of an episode affected the number of weekly reports per episode. The model estimated that the PCV was associated with a 1.1 week decrease compared to the Hib vaccine and that antibiotic use was associated with a 0.6 week decrease. Even though these estimates were not statistically significant, they are somewhat consistent with the findings of other studies. A meta-analysis found that antibiotic treatment for children with AOM decreased occurrences of TM perforation (number needed to treat: 33), so it is plausible that antibiotics might also decrease the duration of ear drainage due AOM with TM perforation. Three large RCTs have found that the PCV caused a relative risk reduction (RRR) of 6-34% in the incidence of AOM episodes in children, so it is plausible that the PCV might also decrease the duration of episodes of AOM with TM perforation.

**Strengths**

This analysis has several strengths. Its data come from a blinded, randomized trial. Furthermore, the comparison of the baseline participant characteristics in Table 2 indicates that randomization was effective overall. The characteristics that differed most between the two groups were prematurity, cesarean section birth, and secondhand smoke exposure. Since prematurity and cesarean section birth are not known risk factors for otitis media, the modest differences for those characteristics are unlikely to have substantially affected the results.
Secondhand smoke exposure is a known contributor to otitis media, but the 6.2% difference (11 more infants in the PCV group) is also unlikely to have substantially affected the results. A recent meta-analysis estimated that the increased risk of otitis media due to secondhand smoke exposure was relatively small with an odds ratio of 1.37 (95% CI, 1.25-1.50). Based on this odds ratio and the incidence of episodes in the analysis, the 6.2% difference in secondhand smoke exposure would contribute an estimated 0.3 additional episodes to the PCV group, which would not have significantly affected the results. In addition, there were similar percentages of secondhand smoke exposure among infants with AOM with TM perforation in both the PCV and Hib vaccine groups (Table 8).

Additional strengths of this analysis are that data were collected prospectively and that there were low numbers of infants lost to follow up and a high level of data completeness. Specifically, 99% of weekly interviews were completed, 2.4% of infants were lost to follow up after the intervention began, and 5.9% of infants total were lost to follow up. Data completeness and number of infants lost to follow up were similar for both groups.

**Limitations**

This analysis has many limitations that primarily involve issues with study design, measurement, recordkeeping, and implementation. The limitations are grouped into those categories and described below.

**Limitations due to Study Design**

The data in this analysis were collected for the Mother’s Gift trial, which did not have a true control group. Due to a request by the ICDDR,B IRB, infants in the non-experimental group were also given a vaccine. Trial authors chose the Hib conjugate vaccine, Hiberix® (GlaxoSmithKline), to be the quasi-placebo for the control group. Other studies have also given
quasi-placebos to control group participants,\textsuperscript{46} including a similar study that investigated the effect of PCV on AOM, using the hepatitis A vaccine as a quasi-placebo.\textsuperscript{28} The use of the Hib vaccine as a quasi-placebo is a limitation of this analysis because Hib is a known pathogen in otitis media. However, it is a minor pathogen, which makes it less likely to have a substantial effect on the results, as is outlined in detail below.

Haemophilus influenzae bacteria can be divided into two kinds: unencapsulated (which are referred to as nontypeable) and encapsulated (which are divided into serotypes a–f, with Hib being serotype b). Nontypeable Haemophilus influenzae (NTHi) strains mostly cause infections of the upper and lower respiratory tract, including otitis media. NTHi are responsible for about 12-30\% of cases of otitis media, second only to Streptococcus pneumoniae.\textsuperscript{14,27,28,37} The Hib vaccine is not effective against NTHi and the infections they cause. The immunogenic component of the Hib conjugate vaccine is polyribosylribitol phosphate, the polysaccharide contained in the Hib capsule. Since NTHi do not have a capsule, the Hib conjugate vaccine in not effective on them.

Hib was a common cause of invasive infections such as meningitis, pneumonia, septic arthritis, cellulitis, and bacteremia prior to widespread Hib vaccination. In populations not immunized against Hib, it still is a common cause of those infections. Hib is a minor cause of otitis media, responsible for 0.6\% of episodes in populations immunized against Hib and for 1-3\% of episodes prior to widespread Hib vaccination.\textsuperscript{27,28,37} Since the Hib vaccine is not effective against NTHi and since Hib is responsible for a very small percentage of otitis media episodes, the Hib vaccine is considered as a quasi-placebo in the interpretation of this analysis. If using the Hib vaccine as a quasi-placebo were to affect the results, it would most likely cause a small decrease in the differences in otitis media between the two groups, creating a small bias toward
the null hypothesis. Although it is reasonable to consider the Hib vaccine as a quasi-placebo, this presumption is vulnerable to an unknown degree of uncertainty, given the complexity and incomplete understanding on a microbiological level of exactly how and why bacterial ear infections develop.

The small sample size and short duration of observation limited the potential of this analysis to detect the effect of the PCV on AOM with TM perforation. The total observation time for this analysis was 117 child-years. By contrast, the three other randomized trials that have investigated the effect of the PCV on otitis media had 2,400 child-years, 10,000 child years, and 130,000 child years.28,34,44 The relatively short total period of observation resulted in a small number of episodes in the analysis and limited its power to detect differences in both the incidence and duration of episodes of AOM with TM perforation.

Reliable data collection for this analysis ended at about 5.5 months (24 weeks) of age. This was inappropriately early for the outcome of interest, and it further limited the ability of the analysis to detect the effects of the PCV. Studies in both high and low-income countries have found that the incidence of AOM with and without TM perforation is greatest between 6-24 months of age.34,47 The 0-6 month period accounts for only about 15-17% of episodes of AOM between 0-24 months of age and about 10% of episodes between 0-48 months of age.34,47 Only having reliable data through 5.5 months of age meant that the analysis lacked data for the periods when its participants would experience the vast majority of episodes of AOM with TM perforation.

This analysis was undertaken because a post-hoc examination of the interview data uncovered a statistically significant difference in the weekly reports of AOM with TM perforation the PCV and Hib vaccine groups. This increases the possibility of that finding being
due to a type 1 error. However, that difference was not statistically significant after adjustment for confounding due to discrepancies in antibiotic use between the two groups. As a result, type 1 error ended up not being a concern for this analysis.

**Limitations due to Measurement Issues**

Secondary analyses are vulnerable to measurement errors when the conceptualization and measurement of outcome variables are substantially different from their purposes in the original study. This was especially true of this analysis’ use of caregiver report of ear drainage to represent AOM with TM perforation. This conceptualization increased the likelihood of both underdiagnosis and overdiagnosis.

Diagnosis of AOM with TM perforation by caregiver report would lead to underdiagnosis when caregivers fail to recognize or report ear drainage. This analysis had a much lower incidence of AOM with TM perforation than a comparable study, and it also had a significant difference in incidence between male and female infants. Underdiagnosis was a likely contributor to both of these findings.

The incidence of AOM with TM perforation in this analysis was much lower compared to a study in rural Bangladesh by Roy et al., which used more deliberate measurement techniques. That study found an incidence of 0.54 episodes per child year between 0-6 months. This analysis found an incidence of 0.20 episodes per child year between the similar age range of 6-24 weeks. This discrepancy is most likely due to the more sensitive measurement techniques in the Roy et al. study, in which interviews and otoscopy were performed every 4 days with the explicit purpose of screening for AOM both with and without perforation. An actual difference in incidence between urban and rural populations may have also contributed to the discrepancy.
between the two studies. Differences in incidence between urban and rural populations have
described in other studies and attributed to environmental and socio-economic factors.48-50

The analysis found that females were 3.9 times less likely than males to have an episode
of AOM with TM perforation (Table 6). A similar phenomenon was noted in another study in
Bangladesh, which found that caregivers were 1.7 times less likely to seek medical treatment for
their female children than their male children.51 Underdiagnosis of female infants, as opposed to
overdiagnosis of males, is the more likely explanation for this finding, given the relatively low
overall incidence of episodes of AOM with TM perforation in this analysis. The difference in
incidence between males and females could also be partially explained by an actual difference in
the epidemiology of otitis media. Roy et al. found that the incidence of AOM with TM
perforation was similar for males and females in rural Bangladesh, but they did find that males
were more likely to have recurrent episodes.47 Several large epidemiologic studies in high-
income countries have found that males are at a slightly increased risk for otitis media.34,52-55
Although this might partially explain the large difference in incidence between males and
females in this analysis, it is very unlikely that it would explain all or even most of it.

Using caregiver report of ear drainage to represent AOM with TM perforation could also
lead to overdiagnosis because it does not distinguish AOM with TM perforation from the other
common causes of ear drainage in infants, such as otitis externa, foreign body in the ear canal,
and normal drainage of cerumen. Table 11 describes the expected findings for each of these
conditions. In clinical practice, the determination of the specific cause of ear drainage is based
on a combination of the appearance of the ear drainage, otoscopy, and clinical history. Had the
weekly interviews included questions about the ear drainage and other relevant symptoms, the
analysis could have more accurately determined when ear drainage was AOM with TM
perforation and when it was not. For example, cerumen could have been easily excluded as the cause of ear drainage with a few simple questions about the appearance, amount, duration, and frequency of the ear drainage. Overall, using caregiver report of the presence of ear drainage for diagnosis increased the possibility that this analysis overestimated the incidence of AOM with TM perforation.

Relying on caregiver report of ear drainage to diagnose AOM with TM perforation would not necessarily lead to a differential bias in the results because this approach appears to have been employed equally in both groups. However, its potential to cause substantial measurement inaccuracies could still bias the results. For example, the infants represented in rows 8 and 10 in Figure 3 accounted for 15 of the 31 weekly reports of AOM with TM perforation in the Hib vaccine group, which was almost all of the difference in weekly reports between the two groups (See Table 5.). If instead of having AOM with TM perforation, one of these two infants had frequent ceruminous ear drainage and the other infant actually had otitis externa or a foreign body in his/her canal, then overdiagnosis could be the source of almost all the difference between the groups. Normally adequate randomization protects against this sort of phenomenon. However, when the potential for measurement error is this high and when only two participants account for almost all of the difference between the two groups, randomization may not prevent measurement errors from biasing the results.

Other studies diagnose AOM with or without TM perforation using a variety of techniques, which generally seem more reliable than caregiver report of ear drainage. Perkins et al. gave basic physical diagnosis training to high school-educated community health workers (CHWs) in Kenya. After their training, the CHWs could accurately diagnose purulent ear drainage with a specificity and sensitivity of ≥ 95% compared to physician diagnosis. In the
study in rural Bangladesh by Roy et al. that is described above, CHWs were trained for 2 weeks in clinical diagnosis of AOM including otoscopy, and then they diagnosed AOM with TM perforation based on the presence of purulent ear drainage.47 Studies in high-income countries have based diagnosis on a combination of ear fluid cultures and physician examination using standardized criteria.14,28,35 These different techniques are probably much more accurate and reliable than those used in the current analysis.

One other limitation of this analysis due to a measurement issue is interview lateness. 2.6% of the data were collected during interviews that involved recall of information from greater than 7 days prior. Since the average lateness of the interviews was similar in both groups, this should not cause a differential bias. None of the reports of AOM with TM perforation were from late interviews, so lateness did not contribute to overdiagnosis. However, since some caregivers may have forgotten about episodes of ear drainage when more than a week passed between the episode and the next interview, late interviews may have contributed to underdiagnosis.

Limitations due to Recordkeeping and Implementation

At the time of this analysis some of the important data from the original Mother’s Gift trial were unable to be located. The most important of these were clinic records, which had information about when infants received their vaccines and experienced adverse events, such as illnesses requiring hospitalization.

Caregiver reports of vaccine administration in the weekly interviews were used in place of the missing clinic records. It is unclear if these reports are similar in accuracy to the clinic data or not. Figure 2 lists how many infants received each number of doses of their assigned vaccine. The numbers for both groups were remarkably similar. All infants were supposed to
receive three doses of their assigned vaccine. However, according to the caregiver reports, among the infants in the PCV group 10% (17/165) received three doses and 71% (116/165) received two doses. Three doses are needed to generate protective antibody titers against all serotypes of the 7-valent PCV, but two doses do provide protection against 3 serotypes and partial protection against 2 additional serotypes. This apparent suboptimal adherence to the intervention has the potential to cause a bias toward the null hypothesis with respect to the effect of the PCV on AOM with TM perforation. Many previous studies have confirmed the safety of the PCV and Hib vaccines. As a result, there is no reason to expect any differences in hospitalizations or other adverse events between the two groups. Never the less, it is unfortunate that actual data on adverse events was not available for this analysis.

**Interpretation and Generalizability of the Results**

The results of this analysis suggest that the 7-valent PCV does not affect the incidence or duration of episodes of AOM with TM perforation among infants in Bangladesh. However, there is a high degree of uncertainty in these findings due to the problems with study design, measurement, and implementation described above. Due to these issues, the analysis likely has poor internal validity and subsequent low generalizability, such that its results should not be used to draw conclusions about the effect of the PCV on otitis media in any population.

The most serious limitation of the study is the conceptualization and measurement of the main outcome, AOM with TM perforation. The potential for measurement errors from both overdiagnosis and underdiagnosis is so substantial that it raises serious doubts about the accuracy of the results. Several other limitations of the analysis reduce its ability to detect the effect of the PCV on AOM with TM perforation. Some of these are potential sources of bias toward the null hypothesis, such as the high percentage of infants who did not receive three doses of the PCV.
and also the use of the Hib vaccine in the comparison group instead of a true placebo. The relatively small sample size and short duration of data collection render the analysis inadequately powered to identify differences due to the PCV. Having reliable data for only 6–24 weeks of age, a period when the incidence of AOM with TM perforation is among the lowest, made it even more difficult for the analysis to discern whether any statistically significant differences are caused by the PCV.

Taken together these issues suggest that this analysis has poor internal validity, making it is difficult to determine whether the finding that the PCV does not cause a statistically significant difference in AOM with TM perforation is from the limitations of the analysis or is an accurate reflection of the truth for the study population. As a result, no broader conclusions should be made from the results of this analysis and they should be considered to have little or no generalizability.

**Recommendations for Future Research**

This analysis set out to determine what effect the PCV has on the incidence and duration of episodes of AOM with TM perforation among infants in Bangladesh. The analysis was unable to provide an acceptable answer to this question due to problems with internal validity. However, this question is still worth investigating as it is relevant to efforts to determine whether expansion of PCV coverage in India, China, and Indonesia might be beneficial and whether the PCV might be an effective strategy to reduce otitis media in countries where it causes high levels of morbidity and mortality.

On March 21, 2015, Bangladesh introduced a 10-valent PCV into its national immunization program. Although this makes it difficult, if not impossible, to conduct a placebo-controlled RCT on the effects of the PCV on otitis media in Bangladesh, it does create
new opportunities to examine this through some potentially valuable observational studies. One example is a historical cohort study comparing otitis media before and after PCV introduction in Bangladesh. Another example is a prospective cohort study comparing a group in Bangladesh to one in India that is as similar as possible except for not having universal immunization with the PCV. These sorts of studies will not have the benefit of the randomized data that this analysis had. Never the less, their results could be very helpful in determining the effect of PCV on otitis media in area with a high burden of disease. Furthermore, investigation of this issue probably does not merit the significant expense that would likely be associated with conducting a new RCT to investigate this issue. As a result, an observational study is probably the most appropriate type at this point.

A historical cohort study comparing the effect of the newly-introduced 10-valent PCV on IPD is actually currently underway in the Sylhet district of Bangladesh. Coincidentally, the researchers conducting that study are from the same institutions that conducted the Mother’s Gift trial, the ICDDR,B and the Bloomberg School of Public Health at Johns Hopkins University. Including outcomes relevant to otitis media in a study like that one would be the most efficient way to answer the question investigated in this analysis. Such an approach should attempt to avoid the limitations encountered in this analysis, which it could do by achieving a high level of adherence to the PCV schedule, using valid and accurate measurement techniques, limiting confounding variables as much as possible, and ensuring adequate sample size and appropriate timing and duration of data collection.

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Steinhoff, who receives research support from the Bill and Melinda Gates Foundation, USAID, the Thrasher Fund, Wyeth, GlaxoSmithKline, Sanofi-Aventis, and Merck and lecture fees from GlaxoSmithKline and Sanofi-Aventis.

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Table 1. Maternal-Infant Vaccine Combinations

<table>
<thead>
<tr>
<th>Maternal Vaccine:</th>
<th>4 Possible Vaccine Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV</td>
<td>PPV</td>
</tr>
<tr>
<td>Hib</td>
<td>PCV</td>
</tr>
<tr>
<td>Influenza</td>
<td>Hib</td>
</tr>
<tr>
<td>PCV</td>
<td>PCV</td>
</tr>
</tbody>
</table>

Figure 1. Group and Vaccine Assignments

Pregnant mothers and their future infants randomized (n = 340 pairs)

3rd Trimester maternal vaccine:
Pneumococcal polysaccharide (n = 168)

Infant vaccine:
- Pneumococcal conjugate (n = 86)

3rd Trimester maternal vaccine:
Inactivated influenza (n = 172)

Infant vaccine:
- H. influenzae type b (n = 82)

Infant vaccine:
- Pneumococcal conjugate (n = 85)

Infant vaccine:
- H. influenzae type b (n = 87)

- Pneumococcal conjugate vaccine (PCV) group (n = 171)
- Haemophilus influenzae type B (Hib) vaccine group (n = 169)
823 pregnant women were assessed for eligibility

- 272 declined to participate
- 185 were not eligible based on the inclusion or exclusion criteria
  - 77 were not planning to stay in the area after delivery.
  - 68 had a previous history of systemic illness, pregnancy complication, preterm delivery, abortion, or birth with a congenital anomaly.
  - 17 had a mismatch between their LMP and the clinical examination.
  - 17 had a history of an allergic reaction to a vaccine
  - 6 had a contraindication to a study vaccine.
- 77 were not planning to stay in the area after delivery.

340 pairs of pregnant women and their future infants were enrolled and randomized

PCV Group: (n = 171 infants)

- 6 infants left the study prior to the intervention:
  - 2 pregnant mothers (and their future infants) were lost to follow up before delivery*
  - 2 stillbirths
  - 1 neonatal death (at 2 days of age)
  - 2 infants lost to follow-up between delivery and 6 weeks of age*

- 165 infants were assigned to receive 3 doses of the PCV.
  - 3 received 0 doses
  - 29 received 1 dose
  - 116 received 2 doses
  - 15 received 3 doses
  - 2 received 4 doses

- 162 infants completed data collection through 24 weeks.
  - 3 infants left the study prior to completion of data collection (12, 19, and 20 weeks).*

- 165 infants had partial or complete data that was included in the analysis.

Hib Vaccine Group: (n = 169 infants)

- 6 infants left the study prior to the intervention:
  - 2 pregnant mothers (and their future infants) were lost to follow up before delivery*
  - 1 stillbirth
  - 2 neonatal deaths (at 3 and 19 days of age)
  - 1 infant lost to follow-up between delivery and 6 weeks of age*

- 163 infants were assigned to receive 3 doses of the Hib vaccine.
  - 4 received 0 doses
  - 30 received 1 dose
  - 118 received 2 doses
  - 11 received 3 doses

- 158 infants completed data collection through 24 weeks.
  - 5 infants left the study prior to completion of data collection (7, 13, 14, 15, and 22 weeks).*

- 163 infants had partial or complete data that was included in the analysis.

*The reasons that participants were lost to follow up are unknown.
### Table 2. Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PCV Group 165</th>
<th>Hib Vaccine Group 163</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (kg)</td>
<td>3.14</td>
<td>3.02</td>
</tr>
<tr>
<td>Birth weight &lt; 2.5kg (%)</td>
<td>5.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Birth height (cm)</td>
<td>48.7</td>
<td>49.1</td>
</tr>
<tr>
<td>Gestational age at birth (weeks)</td>
<td>39.4</td>
<td>39.6</td>
</tr>
<tr>
<td>Gestational age &lt;38 weeks (%)</td>
<td>15.2*</td>
<td>11.1*</td>
</tr>
<tr>
<td>Mean Apgar score at 1 minute</td>
<td>8.35</td>
<td>8.03</td>
</tr>
<tr>
<td>Mean Apgar score at 5 minutes</td>
<td>9.44</td>
<td>9.28</td>
</tr>
<tr>
<td>Sex of infant is female (%)</td>
<td>44.8</td>
<td>42.3</td>
</tr>
<tr>
<td>Infant born in a hospital or clinic (%)</td>
<td>94.5</td>
<td>89.6</td>
</tr>
<tr>
<td>Infant born by Cesarean delivery (%)</td>
<td>53.9*</td>
<td>39.9*</td>
</tr>
<tr>
<td>Maternal Age (years)</td>
<td>25.2</td>
<td>25.0</td>
</tr>
<tr>
<td>Maternal height (cm)</td>
<td>153</td>
<td>153</td>
</tr>
<tr>
<td>Maternal MUAC (mm)</td>
<td>266</td>
<td>260</td>
</tr>
<tr>
<td>Maternal Gravidaity</td>
<td>2.09</td>
<td>1.88</td>
</tr>
<tr>
<td>Maternal Parity at enrollment (%)</td>
<td>0.66</td>
<td>0.60</td>
</tr>
<tr>
<td>Maternal education (years)</td>
<td>11.3</td>
<td>11.0</td>
</tr>
<tr>
<td>Family owns house (%)</td>
<td>34.5</td>
<td>30.1</td>
</tr>
<tr>
<td>Number of rooms in family home</td>
<td>3.76</td>
<td>3.52</td>
</tr>
<tr>
<td>Someone who lives with the infant smokes (%)</td>
<td>46.1*</td>
<td>39.9*</td>
</tr>
</tbody>
</table>

* Relative difference of >15% between the two groups

### Table 3. Interview Timeliness by Group

<table>
<thead>
<tr>
<th>Timeliness of interviews</th>
<th>PCV Group</th>
<th>Hib Vaccine Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not late</td>
<td>3015 (97.7%)</td>
<td>2933 (97.1%)</td>
</tr>
<tr>
<td>1 week late</td>
<td>35 (1.1%)</td>
<td>31 (1.0%)</td>
</tr>
<tr>
<td>2 weeks late</td>
<td>16 (0.5%)</td>
<td>28 (0.9%)</td>
</tr>
<tr>
<td>3 weeks late</td>
<td>13 (0.4%)</td>
<td>12 (0.4%)</td>
</tr>
<tr>
<td>≥4 weeks late</td>
<td>6 (0.2%)</td>
<td>16 (0.5%)</td>
</tr>
</tbody>
</table>

### Table 4. Interviews and Positive Weekly Reports by Interview Type and Group

<table>
<thead>
<tr>
<th>Interview Type</th>
<th>All interviews by group and type</th>
<th>Positive weekly reports by group and type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCV Group</td>
<td>Hib Vaccine Group</td>
</tr>
<tr>
<td>Telephone</td>
<td>1539 (50%)</td>
<td>1365 (45%)</td>
</tr>
<tr>
<td>Home Visit</td>
<td>1223 (40%)</td>
<td>1385 (46%)</td>
</tr>
<tr>
<td>Clinic Visit</td>
<td>324 (10%)</td>
<td>270 (9%)</td>
</tr>
<tr>
<td></td>
<td>4 (31%)</td>
<td>4 (13%)</td>
</tr>
</tbody>
</table>
Figure 3. Weekly Reports of AOM with TM Perforation by Week, Infant, Group and Antibiotics

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Infants</th>
<th>Weeks with positive reports of AOM with TM perforation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hib Vaccine Group</td>
<td></td>
<td>6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
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<tr>
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<td>4</td>
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<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCV Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
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<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **AOM with TM perforation was reported, but antibiotic use was not reported**
- **AOM with TM perforation and antibiotic treatment for AOM were both reported**
- **AOM with TM perforation and antibiotic treatment for a respiratory infection were both reported**

Table 5. AOM with TM Perforation by Group

<table>
<thead>
<tr>
<th></th>
<th>PCV Group</th>
<th>Hib Vaccine Group</th>
<th>Risk Difference (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants included in the analysis</td>
<td>165</td>
<td>163</td>
<td></td>
</tr>
<tr>
<td>Number of weekly interviews</td>
<td>3086</td>
<td>3020</td>
<td></td>
</tr>
<tr>
<td>Number of weekly reports of AOM with TM perforation</td>
<td>13</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Number of infants with ≥ 1 episode of AOM with TM perforation</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Number of episodes of AOM with TM perforation</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Percentage of weeks with a positive report of AOM with TM perforation</td>
<td>0.4% (13/3086)</td>
<td>1.0% (31/3020)</td>
<td><strong>0.6%</strong> (0.2% – 1.0%)</td>
</tr>
<tr>
<td>Percentage of infants with at least one positive report of AOM with TM perforation</td>
<td>5.4% (9/165)</td>
<td>6.1% (10/163)</td>
<td><strong>0.7%</strong> (-4% – 6%)</td>
</tr>
<tr>
<td>Percentage of weeks with a report of a new episode of AOM with TM perforation</td>
<td>0.36% (11/3086)</td>
<td>0.40% (12/3020)</td>
<td><strong>0.04%</strong> (-0.3% – 0.3%)</td>
</tr>
</tbody>
</table>

*Bold value is statistically significant since the confidence interval does not include zero.*
Table 6. Episodes of AOM with TM perforation by Sex of Infants

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
<th>Risk Difference (95% C.I.)</th>
<th>Relative Risk (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of infants in the entire study with ≥ 1 episode of AOM with TM perforation</td>
<td>2.1% (3/165)</td>
<td>8.0% (16/201)</td>
<td><strong>5.9% (1.5% – 10%)</strong></td>
<td><strong>3.9 (1.2 – 13)</strong></td>
</tr>
<tr>
<td>Percentage of infants in the PCV group with ≥ 1 episode of AOM with TM perforation</td>
<td>1.4% (1/74)</td>
<td>8.8% (8/91)</td>
<td><strong>7.4% (1.1% – 13%)</strong></td>
<td><strong>6.5 (0.8 – 51)</strong></td>
</tr>
<tr>
<td>Percentage of infants in the Hib vaccine group with ≥ 1 episode of AOM with TM perforation</td>
<td>2.9% (2/67)</td>
<td>8.5% (8/94)</td>
<td>5.6% (-1.3% – 13%)</td>
<td><strong>2.9</strong></td>
</tr>
</tbody>
</table>

*Bold values are statistically significant

Table 7. Number of Weekly Reports per Episode by Group

<table>
<thead>
<tr>
<th></th>
<th>PCV Group</th>
<th>Hib Vaccine Group</th>
<th>/z/ statistic*</th>
<th>p = *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of weekly reports AOM with TM perforation per episode</td>
<td>1.2 (13/11)</td>
<td>2.6 (31/12)</td>
<td>2.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Median number of weekly reports AOM with TM perforation per episode (with range)</td>
<td>1 (1-2)</td>
<td>2 (1-6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* From Wilcoxon rank-sum test

Table 8. Smoke Exposure by Group among Infants with AOM with TM Perforation

<table>
<thead>
<tr>
<th></th>
<th>PCV Group</th>
<th>Hib Vaccine Group</th>
<th>Risk Difference (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of infants with at least one report of AOM with TM perforation exposed to secondhand smoke at home</td>
<td>44% (4/9)</td>
<td>50% (5/10)</td>
<td>6% (-39% – 50%)</td>
</tr>
<tr>
<td>Percentage of episodes of AOM with TM perforation among infants exposed to secondhand smoke at home</td>
<td>46% (6/13)</td>
<td>55% (17/31)</td>
<td>9% (-24% – 41%)</td>
</tr>
</tbody>
</table>

Table 9. Antibiotic Treatment by Group among Infants with AOM with TM Perforation

<table>
<thead>
<tr>
<th></th>
<th>PCV Group</th>
<th>Hib Vaccine Group</th>
<th>Risk Difference (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of reports of AOM with TM perforation with which antibiotic treatment was also reported</td>
<td>85% (11/13)</td>
<td>52% (16/31)</td>
<td><em><em>33%</em> (7% – 59%)</em>*</td>
</tr>
<tr>
<td>Percentage of episodes of AOM with TM perforation with which antibiotic treatment was reported during the first week of the episode</td>
<td>82% (9/11)</td>
<td>25% (3/12)</td>
<td><em><em>57%</em> (23% – 90%)</em>*</td>
</tr>
</tbody>
</table>

*Bold values are statistically significant since the confidence interval does not include zero.
Table 10. Weekly Reports per Episode by Vaccine Group and Antibiotic Treatment during First Week

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>t Value</th>
<th>p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>1.1</td>
<td>1.7</td>
<td>0.10</td>
</tr>
<tr>
<td>Antibiotic treatment during the first week of the episode</td>
<td>0.61</td>
<td>1.0</td>
<td>0.33</td>
</tr>
</tbody>
</table>

* Based on Generalized Linear Model

Table 11. Common Causes of Ear Drainage in Infants

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ear Drainage</th>
<th>Otoscopy</th>
<th>Clinical History (Possible Symptoms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOM with TM Perforation</td>
<td>Purulent</td>
<td>Perforated TM, which may be obscured by drainage.</td>
<td>Recent or current fevers, runny nose, cough, and/or congestion. Apparent otalgia.</td>
</tr>
<tr>
<td>Otitis Externa</td>
<td>Purulent or serous</td>
<td>Intact TM. Inflammation along external auditory canal.</td>
<td>Apparent otalgia.</td>
</tr>
<tr>
<td>Foreign body</td>
<td>Purulent, serous, and/or bloody</td>
<td>Intact TM. Foreign body in external auditory canal.</td>
<td>Something placed in the ear or has an older sibling. May have fever and apparent otalgia.</td>
</tr>
<tr>
<td>Cerumen</td>
<td>Yellow or brown-tinged, waxy</td>
<td>Intact TM. Cerumen in external auditory canal.</td>
<td>Asymptomatic. No apparent otalgia.</td>
</tr>
</tbody>
</table>
APPENDIX A: Otitis Media Terminology and Definitions

Otitis media literally means inflammation of the middle ear. It is a general term for a closely related group of disorders involving the middle ear.\textsuperscript{62,63} Many terms have been used to describe the different types of otitis media, resulting in confusion and misunderstanding among medical providers and researchers.\textsuperscript{63} Despite growing consensus regarding terminology and definitions, significant differences still persist.\textsuperscript{36,63-66} The analysis described in this master’s paper focuses on one type of otitis media, AOM with TM perforation. The types of otitis media relevant to this paper are displayed in Figure A1 and described below.

Figure A1. Relationships between common types of otitis media and tympanic membrane perforations\textsuperscript{29,63,64,67}

![Diagram of relationships between types of otitis media and tympanic membrane perforations]

\*The three italicized conditions in the lower right quadrant of the figure are not types of otitis media, but they are included because they are closely related to the other conditions in the figure.

Acute otitis media (AOM) is defined as the rapid onset of signs and symptoms of a middle ear infection, such as otalgia, fever, and a bulging TM.\textsuperscript{63,64} The diagnosis of AOM is based on clinical findings, and it does not differentiate between bacterial and viral causes.\textsuperscript{64}

Otitis media with effusion (OME) is defined as middle ear inflammation with accumulation of fluid in the middle ear without signs and symptoms of an acute infection.\textsuperscript{63,64} As depicted in Figure A1, OME can become AOM, if an acute infection develops.\textsuperscript{65} Conversely, AOM can become OME, if the signs and symptoms of acute infection resolve and fluid remains in the middle ear.\textsuperscript{64,65}
AOM with TM perforation is the term for an acute infection of the middle ear that results in purulent otorrhea through a perforated TM, regardless of the cause of the perforation.\textsuperscript{63,66} (Some refer to this simply as AOM with perforation.\textsuperscript{63}) TM perforation occurs most commonly as a complication of AOM.\textsuperscript{63,68} When TM perforation occurs due to OME or trauma, it can heal spontaneously, persist as a chronic TM perforation, or become infected leading to AOM with TM perforation.\textsuperscript{36,63,68}

When complete resolution of AOM with TM perforation does not occur, it progresses to one of the two chronic conditions in Figure A1.\textsuperscript{63} If the middle ear infection resolves, but the TM does not heal, then it becomes a chronic TM perforation.\textsuperscript{63} When all the features of AOM with TM perforation continue for greater than 6 weeks, then it is considered chronic suppurative otitis media (CSOM), which is persistent middle ear inflammation, TM perforation, and purulent otorrhea.\textsuperscript{36,63} CSOM is subdivided into active and inactive types depending on whether otorrhea is currently present or not.\textsuperscript{36,63} CSOM is notable because it is responsible for most of the morbidity and mortality due to otitis media worldwide.\textsuperscript{29,36} AOM with TM perforation, which is the primary focus of this analysis, is significant in large part because it is the main precursor condition to CSOM.
APPENDIX B: Burden of Suffering due to Otitis Media

Otitis media is important on both the individual health and public health levels. Although the various types of otitis media can often resolve spontaneously or with a course of antibiotics, they can sometimes lead to serious complications. This appendix describes the significant complications of otitis media, reviews a select group of studies on the complications of otitis media, and summarizes the global and regional estimates of morbidity and mortality due to otitis media.

Complications of Otitis Media

Most often, complications from otitis media occur when bacterial infections in the middle ear spread to adjacent ear and central nervous system structures resulting in damage to and dysfunction of those structures. Complications are often divided into two groups, intratemporal and intracranial. Intratemporal complications include conductive and sensorineural hearing impairment (HI), cholesteatoma, facial nerve paralysis, labyrinthitis, mastoid abscess, mastoiditis, ossicular discontinuity, and vestibular dysfunction. Intracranial complications include brain abscess, cerebral venous sinus thrombosis, epidural abscess, meningitis, otitic hydrocephalus, perisinus abscess, and subdural empyema. The one routinely occurring complication that is neither intratemporal nor intracranial is sternocleidomastoid abscess (Bezold’s abscess). Although otitis media often resolves without causing serious complications, individuals with the above sequelae can experience significant short-term disability, long-term disability, and even death.

Evidence for the common complications of otitis media listed above comes mostly from retrospective chart reviews of patients who were seen at otolaryngology clinics or admitted to otolaryngology services at tertiary care hospitals. Most of the publications are single case
reports, case series, cross-sectional studies, or case-control studies. A systematic search of PubMed, Ovid MEDLINE, and Cochrane Databases by Jung et al. found 127 relevant studies published just between 2007 and 2011. 84 Thorough reviewing of that many articles is beyond the scope of this paper, but I did perform a focused PubMed search was performed to investigate the complications of otitis media. A search for “otitis media,” “complications,” and “intracranial,” limited to articles published after 1990, in English, and with human subjects, yielded 288. Review of the titles and abstracts of those 288 articles identified 36 relevant articles. I chose to further narrow the results by only including studies with ≥20 subjects with intracranial complications to capture a greater number of subjects with serious complications. This yielded 13 studies for in-depth review. 74-78,81-83,85-89 Review of those articles uncovered 2 additional articles that were appropriate to include in this in-depth review. 31,80

The studies included patient data from as early as 1978. Based on the World Bank classification method, fourteen of the studies are from middle income countries, and one is from a high income country. 31,74-83,85-90 Seven of the studies include patients with otitis media with and without complications. 31,75,76,78,81,85,86 Eight of them are case series of only patients with complications. 74,77,80,82,83,87-89 Nine of the studies only include patients with CSOM. 31,76-78,80,82,87-89 My review of these studies yielded a few interesting observations.

Several studies reported whether patients’ complications were due to AOM or CSOM. Among 422 subjects in Egypt with intracranial and/or extracranial complications, 98% had CSOM and 2% had AOM. 85 Among 285 subjects in China with intracranial and/or extracranial complications, 96% had CSOM and 4% had AOM. 86 Among 102 subjects in Thailand with intracranial and/or extracranial complications, 90% had CSOM and 10% had AOM. 75 About half of those subjects were also included in a study of 87 patients in Thailand with intracranial
complications, of whom 94% had CSOM and 6% had AOM. Among 33 patients in Brazil with intracranial complications, 82% had CSOM and 18% had AOM. Results from these studies support the expert opinion that most of the morbidity and mortality from otitis media is due to CSOM. Conversely, the one study from a high income country, Israel, reported that among the 28 patients with intracranial complications, 29% had ASOM and 71% had AOM. This is likely because CSOM is less frequent in Israel, which like most other high-income countries, is classified in the lowest CSOM prevalence category (<1%) by the WHO.

The fifteen studies described a total of 986 subjects with intracranial complications due to otitis media, most of whom also had intratemporal complications. There were 86 deaths (8.7%) among these subjects. By contrast, there were no deaths noted among the 1,522 subjects with only intratemporal complications of otitis media in these studies. The mortality rates varied greatly between the studies. The highest mortality for intracranial complications was reported in studies from New Guinea (31%, 10/33), Turkey (26%, 15/57), and Thailand (18%, 16/87). The lowest mortality was reported in a different study from Turkey (0%, 0/50) and studies from Israel (0%, 0/28) and Egypt (2.6%, 6/228). Despite the obvious heterogeneity of these studies, they do provide convincing evidence that the overwhelming, if not all, of the deaths due to otitis media occur due its intracranial complications. Brain abscess, meningitis, cerebral venous sinus thrombosis, and subdural empyema were the most commonly mentioned complications leading to the deaths in these studies.

There is significant variability in many aspects of the studies I reviewed. There are multiple explanations of this variability. Study populations were different in the severity of the disease at baseline. Also, the incidence, prevalence, severity and course of otitis media vary
widely between and within countries, depending on numerous factors such as socioeconomic status, environmental conditions, and access to medical care and treatment.\textsuperscript{36}

\textbf{Estimates of Morbidity and Mortality due to Otitis Media}

Several estimates of the worldwide morbidity and mortality due to otitis media have been made by extrapolating from available data using statistical modeling. Since 1990, the World Health Organization (WHO) has been involved in efforts to assess the global burden of disease, publishing estimates of global morbidity and mortality due to about 100 different causes, one of which is otitis media.\textsuperscript{92,93} The WHO global burden of disease estimates are available for 1990, 2000-2002, 2004, 2008 and 2011.\textsuperscript{92} The Institute for Health Metrics and Evaluation (IHME), a research center at the University of Washington, built on the work done by the WHO to produce estimates for 1990 and 2010, which were published in 2012.\textsuperscript{32,94} The IHME collaborated with six other institutions around the world, including the WHO, and provided estimates for 291 different causes of morbidity and mortality.\textsuperscript{32} Monasta et al. provide an estimate for global mortality due specifically to otitis media in 2005.\textsuperscript{29} Table B1 displays all of these estimates, except for the WHO estimates for 2001, 2002, and 2008, which were omitted for the sake of brevity since they were similar to other estimates.

Table B1. Selected estimates for morbidity and mortality due to otitis media

<table>
<thead>
<tr>
<th>Year of Estimate</th>
<th>Author (Publication Date)</th>
<th>Mortality (Deaths per year)</th>
<th>Morbidity (Millions of DALYs per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>WHO (1996)\textsuperscript{93}</td>
<td>28,000</td>
<td>2.2</td>
</tr>
<tr>
<td>1990</td>
<td>IHME (2012)\textsuperscript{1,2}</td>
<td>5,200</td>
<td>4.2</td>
</tr>
<tr>
<td>2000</td>
<td>WHO (2001)\textsuperscript{95}</td>
<td>6,000</td>
<td>1.4</td>
</tr>
<tr>
<td>2000 revised</td>
<td>WHO (2013)\textsuperscript{96,97}</td>
<td>3,500</td>
<td>4.8</td>
</tr>
<tr>
<td>2004</td>
<td>WHO (2008)\textsuperscript{98}</td>
<td>5,000</td>
<td>1.5</td>
</tr>
<tr>
<td>2005</td>
<td>Monasta et al. (2012)\textsuperscript{29}</td>
<td>21,000</td>
<td>Not calculated</td>
</tr>
<tr>
<td>2010</td>
<td>IHME (2012)\textsuperscript{1,2}</td>
<td>3,500</td>
<td>4.7</td>
</tr>
<tr>
<td>2011</td>
<td>WHO (2013)\textsuperscript{96,97}</td>
<td>3,100</td>
<td>5.1</td>
</tr>
<tr>
<td>2013</td>
<td>IHME (2015)\textsuperscript{4}</td>
<td>2,400</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Range of Estimates for Years 1990 – 2011</td>
<td>2,400 to 28,000</td>
<td>1.4 to 5.1</td>
<td></td>
</tr>
</tbody>
</table>
As seen at the bottom of Table B1, there is a wide range for the estimates of morbidity and mortality due to otitis media. Mathers et al. explain that the WHO estimates published prior to 2013 used different methods and data sources.\textsuperscript{99,100} As a result, the changes in the WHO estimates over time could be due to the use of different methods and data sources, actual differences in the level of disease, or a combination of both. Time series comparisons are only valid for the IHME 1990 and 2010 estimates and for the WHO 2000 revised and 2011 estimates.\textsuperscript{32,99,100} Both sets of comparisons show a small decline in deaths and a small increase in DALYs due to otitis media.

**Disparities in the Burden of Suffering due to Otitis Media**

**Age-Related Disparities**

Monasta et al. calculated the one estimate of mortality in due to otitis media in Figure 1 that is not from a larger global burden of disease project. Their study focused specifically on otitis media and calculated global incidence rates for AOM and CSOM, hearing impairment (HI) prevalence and deaths due to otitis media. Their estimates were broken down by age and by the 21 WHO region areas used in the 2010 Global Burden of Disease study.\textsuperscript{29,32} Table B2 illustrates some basis epidemiologic trends with otitis media. AOM and CSOM incidence peak in early childhood, however greater prevalence of CSOM will be seen into adolescence and early adulthood, since the average duration is 1-3 weeks for ASOM and 10 years for CSOM.\textsuperscript{29,101} Prevalence of hearing impairment due to otitis media gradually increases throughout the lifespan. Deaths due to otitis media are greatest among infants, young children, and the elderly.

**Geographic Disparities**

The six WHO region areas whose estimates were above the global average in all four categories were included in Table B3. The other fifteen WHO regions were below the global
average in all four categories. Monasta et al. also estimated that the South Asia WHO region area (Afghanistan, Bangladesh, Bhutan, India, Nepal, and Pakistan), which had 23% of the world’s population, accounted for 48% of the deaths due to otitis media.\textsuperscript{29,32} For hearing impairment (HI) due to otitis media, they estimated that South Asia accounted for 75% of moderate HI, 85% of severe HI, and 93% of profound HI due to otitis media.\textsuperscript{29,33}

Table B2. Global AOM and CSOM incidence, HI prevalence, and deaths for 2005 by age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>AOM % incidence</th>
<th>CSOM % incidence</th>
<th>HI&gt;25dB best ear prevalence per 10,000</th>
<th>Deaths per 10,000,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>45</td>
<td>15</td>
<td>9.3</td>
<td>85</td>
</tr>
<tr>
<td>1–4</td>
<td>61</td>
<td>10</td>
<td>23</td>
<td>91</td>
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<td>5–9</td>
<td>22</td>
<td>8.3</td>
<td>26</td>
<td>39</td>
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<tr>
<td>10–14</td>
<td>19</td>
<td>3.9</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>15–19</td>
<td>3.5</td>
<td>3.4</td>
<td>27</td>
<td>19</td>
</tr>
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<td>20–24</td>
<td>3.1</td>
<td>4.8</td>
<td>30</td>
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<td>25–34</td>
<td>1.6</td>
<td>3.3</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>35–44</td>
<td>1.5</td>
<td>3.2</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>45–54</td>
<td>1.8</td>
<td>4.1</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>55–64</td>
<td>1.9</td>
<td>3.7</td>
<td>40</td>
<td>23</td>
</tr>
<tr>
<td>65–74</td>
<td>2.1</td>
<td>2.5</td>
<td>45</td>
<td>49</td>
</tr>
<tr>
<td>75–84</td>
<td>2.3</td>
<td>2.6</td>
<td>43</td>
<td>156</td>
</tr>
<tr>
<td>85+</td>
<td>2.3</td>
<td>2.7</td>
<td>38</td>
<td>179</td>
</tr>
<tr>
<td>Global mean for all ages</td>
<td>11</td>
<td>4.8</td>
<td>31</td>
<td>33</td>
</tr>
</tbody>
</table>

Adapted from Monasta et al.\textsuperscript{29}

Table B3. AOM and CSOM Incidence, HI Prevalence, and Deaths for 2005 by Selected WHO Region Areas

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>AOM % incidence</th>
<th>CSOM % incidence</th>
<th>HI&gt;25dB best ear prevalence per 10,000</th>
<th>Deaths per 10,000,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia South</td>
<td>15</td>
<td>6.6</td>
<td>97</td>
<td>69</td>
</tr>
<tr>
<td>Oceania</td>
<td>29</td>
<td>9.4</td>
<td>51</td>
<td>101</td>
</tr>
<tr>
<td>SSA Central</td>
<td>43</td>
<td>7.6</td>
<td>30</td>
<td>96</td>
</tr>
<tr>
<td>SSA East</td>
<td>23</td>
<td>6.1</td>
<td>32</td>
<td>73</td>
</tr>
<tr>
<td>SSA South</td>
<td>15</td>
<td>4.8</td>
<td>9.4</td>
<td>34</td>
</tr>
<tr>
<td>SSA West</td>
<td>43</td>
<td>7.2</td>
<td>34</td>
<td>92</td>
</tr>
<tr>
<td>Global mean for all regions</td>
<td>11</td>
<td>4.8</td>
<td>31</td>
<td>33</td>
</tr>
</tbody>
</table>

SSA = Sub-Saharan Africa. Adapted from Monasta et al.\textsuperscript{29}
Economic-Related Disparities

Some of the WHO Global Burden of Disease estimates group together countries by income level and by region, which also reveals disparities in the burden of suffering due to otitis media. These estimates use the World Bank classification system to divide countries into low-income, middle-income, and high-income groups, based on each country’s average per capita gross national income.\textsuperscript{90,102} Low-income and middle-income countries account for about 80% of the world’s population.\textsuperscript{103} However, in the WHO estimates for 2000, 2002, 2004, and 2011, low-income and middle-income countries accounted for 94-96% of deaths and 90-93% of DALYs due to otitis media.\textsuperscript{96-98,104} The WHO figures for 2000 (revised) and 2011 provide estimates for each of the seven World Bank regions.\textsuperscript{90,96,97} Table B4 includes estimates for the three regions with the highest numbers of deaths and DALYs due to otitis media. It shows that South Asia and Sub-Saharan Africa regions account for disproportionally greater shares of the burden of disease due to otitis media relative to their populations.

Table B4. WHO Estimates of Morbidity and Mortality from Otitis Media by Selected World Bank Regions

<table>
<thead>
<tr>
<th>World Bank Region\textsuperscript{90}</th>
<th>Percentage of world population in 2012\textsuperscript{105}</th>
<th>Deaths due to Otitis Media (Percentage of world total)\textsuperscript{96}</th>
<th>DALYs due to Otitis Media (Percentage of world total)\textsuperscript{97}</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Asia and Pacific</td>
<td>28%</td>
<td>10% 10%</td>
<td>29% 26%</td>
</tr>
<tr>
<td>South Asia</td>
<td>23%</td>
<td>35% 26%</td>
<td>28% 28%</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>13%</td>
<td>31% 44%</td>
<td>16% 21%</td>
</tr>
</tbody>
</table>

Methods for Estimating Morbidity and Mortality due to Otitis Media

Murray and Lopez were the senior authors of the IHME estimates, and they were involved in many of the WHO estimates.\textsuperscript{93,99,100} They criticize the WHO estimates for relying on methods that are too subjective.\textsuperscript{32} They argue that the IHME estimates use a more systematic approach.\textsuperscript{32} Alternatively, the WHO has not officially endorsed the IHME results due to
concerns about some substantial differences (not necessarily involving otitis media) between the WHO and IHME estimates.99

The IHME and WHO publications do not discuss the specific source data for otitis media in their methodology,1,2,99,100 but Monasta et al. describe it in detail.29 They identify several significant gaps in the source data, which they deal with through extrapolation and by making assumptions about the nature of AOM and CSOM.29 Worldwide estimates of the burden of disease due to otitis media help put the significance of otitis media in perspective. However, their accuracy is uncertain due to incomplete source data and statistical methodologies dependent on assumptions and extrapolation.
APPENDIX C
Manuscript Prepared for Submission for Publication by Dane Warner and Mark Steinhoff

Clinical Effectiveness of a Pneumococcal Conjugate Vaccine in Acute Suppurative Otitis Media: A Randomized Controlled Trial in Bangladeshi Infants

Otitis media is a significant cause of morbidity and mortality worldwide. According to the World Health Organization (WHO), otitis media was responsible for approximately 5,000 deaths\(^9^8\) and the loss of 1.5 million disability-adjusted life years (DALYs) in 2004.\(^9^8\) This morbidity and mortality are primarily due to the suppurative forms of otitis media, which occur when a middle ear infection is accompanied by tympanic membrane perforation and purulent otorrhea.\(^9^1\) Initially, such an infection is termed acute suppurative otitis media (ASOM).\(^1^0^6\) If the infection and otorrhea persist for more than 2 weeks, it is then considered chronic suppurative otitis media (CSOM), according to the WHO definition.\(^3^6\) CSOM can last for many years, and it is responsible for the vast majority of otitis media complications.\(^9^1\) These include hearing impairments and contiguous and systemic infections, such as mastoiditis, brain abscess, subdural empyema, meningitis, and sepsis.\(^3^6,6^7,9^1\)

Approximately 95% of the morbidity and mortality from otitis media occurs in children in developing countries.\(^9^3\) Africa, South-East Asia, and the Western Pacific account for an estimated 93% of the global disease burden for CSOM.\(^3^6\) The WHO considers a CSOM prevalence of greater than 4% to be a massive public health problem.\(^3^6\) The estimated prevalence rates for these three regions range from 4.2–10%.\(^3^6\) Some ethnic groups have been found to have very high prevalence rates, including Australian Aborigines (15–43%),\(^3^6,6^7,1^0^7\) Inuits (7–46%),\(^6^7,1^0^8\) and some Native American groups (Apache and Navajo, 4–8%).\(^5^0,6^7\) Our study analyzes data collected in Bangladesh, where estimated CSOM prevalence rates range from 7% to 12%.\(^4^7,4^8,1^0^9\)

A study of otitis media incidence in Bangladesh, which followed 252 children from birth to 24 months, reported that 115 children (46%) had at least one episode of otitis media.\(^4^7\) A total of 375 episodes of otitis media were diagnosed by physicians using otoscopy. 14% of the episodes were otitis media without perforation, and 86% were accompanied by otorrhea and classified as ASOM. 5% of the episodes were classified as CSOM, which in this study required a duration of greater than 6 weeks.\(^4^7\)
Efforts to decrease CSOM have included improving environmental conditions, expanding access to medical services, and enhancing health care quality.\textsuperscript{36,50} There is some evidence that these approaches can be effective, but they require significant resources and many years before substantial effects are observed.\textsuperscript{36,50} As a result, there is interest in other strategies for decreasing CSOM and its complications.\textsuperscript{50} Among the possible strategies, immunization has the greatest potential for achieving positive results in areas where there is a high prevalence of CSOM.\textsuperscript{110}

The most common bacteria isolated from otitis media is streptococcus pneumoniae,\textsuperscript{28,35} making it an appropriate target for prevention through immunization. Five randomized controlled trials have investigated the effect of infant immunization with pneumococcal conjugate vaccines (PCVs) on otitis media.\textsuperscript{28,34,35,111,112} They have demonstrated modest reductions in incidence of otitis media, ranging between −1% and 33%, in high resource countries with low rates of CSOM, but a substantial effect on culture proven otitis media caused by streptococcus pneumoniae.\textsuperscript{28,34,35,111,112} None of these studies examined the effect PCVs specifically on ASOM episodes.\textsuperscript{28,34,35,111,112} The only study of PCVs and ASOM in a high CSOM prevalence population was a before/after study that compared an Australian Aboriginal infants born before universal immunization with PCVs to those born afterwards.\textsuperscript{113} The study found no differences in the rates of otitis media without perforation, ASOM or CSOM.\textsuperscript{113} Our study is the only RCT we are aware of that examines the effectiveness of a PCV against ASOM in a population with high ASOM and CSOM prevalence.

**Methods**

**Study Design**

This study is a secondary analysis of data from the Mother’s Gift trial, which investigated the safety and immunogenicity of sequential maternal and infant immunization with pneumococcal vaccines. Mother’s Gift was a prospective, blinded, individually randomized, and comparison-controlled trial (see ClinicalTrials.gov number NCT00142389). The design and results of the Mother’s Gift trial have been previously described.\textsuperscript{16,20}

This secondary analysis examines the effect of infant PCV on acute suppurative otitis media in infants from 10 to 24 weeks of age. Maternal participants were recruited from three urban, antenatal clinics in Dhaka, Bangladesh. All women in their third trimester of pregnancy, who attended one of these three clinics between August 2004 and May 2005, were invited to participate. All data were collected between August 2004 and November 2005. Pregnant
women were excluded from the study if they had a chronic disease, contraindication to a study vaccine, previous or current high-risk pregnancy, previous medical or spontaneous abortion, previous receipt of a study vaccine in the last 3 years, or plans to not live in Dhaka after delivery.

Upon enrollment in the Mother’s Gift trial, the pregnant women and their infants were randomly assigned to one of four groups. Randomization was performed using a computer-generated sequence that was developed centrally before study enrollment began. Randomization was stratified according to clinic and was blocked into four groups. Sequentially-numbered, opaque envelopes with the study group assignments were provided to the three obstetrical clinics. Participants and study staff who collected data were unaware of the study group assignments.

Half of the infants were in the PCV group and received the 7-valent pneumococcal conjugate vaccine (PCV-7) (Prevnar, Wyeth). The other half of the infants were in the Hib group and received the *Haemophilus influenzae* type b (Hib) conjugate vaccine (Hiberix®, GlaxoSmithKline). Pregnant women received either the 23-valent pneumococcal polysaccharide vaccine (PPV) (Pneumovax®, Merck) or the inactivated influenza vaccine (Fluarix®, GlaxoSmithKline). Randomization was designed so that for both the PCV group and the Hib group, one half of the infants had mothers who received the PPV, and the other half had mothers who received the influenza vaccine.\(^{16}\) See Table C1, Patient Characteristics.

Pregnant women received one dose of their assigned vaccine (PPV or influenza vaccine) during the third trimester of pregnancy. Infants received three doses of their assigned vaccine (PCV or Hib vaccine) at 6, 10, and 14 weeks of age. All vaccine doses were administered through intramuscular injection. All study vaccines were purchased from the manufacturers. Clinic staff administering the vaccines were aware of the group assignments, but they were not involved with the measurement of any study outcomes. All other clinic staff and all family members were blinded to group assignments.

The sample size was determined for the purpose of the original Mother’s Gift trial.\(^{16}\) It was powered to detect a difference in the mean pneumococcal antibody titers of the infants. 336 subjects were deemed necessary for the Mother’s Gift trial. This was based on standard formulae, reported local antibody variance data, a 2-sided \(\alpha = 0.05\), a \(\beta = 0.20\), and an assumed 25% attrition rate.\(^{16}\)
The Mother’s Gift trial protocol was reviewed and approved by the institutional review boards at the International Centre for Diarrheal Disease Research, Bangladesh, and the Bloomberg School of Public Health at Johns Hopkins University, Baltimore. Use of study vaccines was approved by the Directorate of Drug Administration of the Government of the People's Republic of Bangladesh. All authors vouch for the completeness of the data and the analyses presented.

**Measurement**

Mothers of the infants were interviewed every week from birth until 24 weeks of age, according to the original study protocol. Interviews were conducted by field workers, who were trained and overseen by study supervisors. Mothers were asked about illness symptoms and infant feeding. Relevant to the current analysis, each mother was asked if her infant had an ear problem during the last week. If the answer was yes, she was asked if there had been drainage from one ear, both ears, or neither ear during the last week. All reports of ear drainage were considered to represent otorrhea due to ASOM. Mothers were also asked what type of treatments they had used for the ear problem. If an infant’s mother was not present, a knowledgeable caregiver was interviewed if one was available.

Monitoring for adverse events was conducted through the weekly interviews. An independent data and safety monitoring board and the institutional review boards in both Bangladesh and Baltimore reviewed all severe adverse events.

**Results**

**Analysis**

PCV does not generate protective antibody titers until after an infant receives its second PCV injection. As a result, this analysis examined data collected from 10 weeks, when the second PCV shot was administered, to 24 weeks or age, when data collection stopped. There were no reports of otorrhea before 10 weeks of age, so no ASOM episodes were excluded from the analysis.

Data regarding ASOM were estimated from weekly reports of otorrhea as follows. Reports of otorrhea separated by one or more weeks without otorrhea were considered to represent distinct episodes of ASOM. Since each weekly report of otorrhea reflected ASOM during part of the previous week, but not necessarily for the whole previous week, the first and last weekly reports of any ASOM episode were assigned an estimated duration of 3.5 days. Any
weekly reports between the first and last weeks were assigned a duration of 7 days, based on the assumption that any consecutive weekly reports represented one continuous episode.

**Participants**

A total of 340 pregnant women met the inclusion criteria and agreed to have their infants participate in the study. All 340 infants were randomized while in utero (PCV group n = 171, Hib group n = 169). Data were available between 10 and 24 weeks for 327 infants (PCV group n = 165, Hib group n = 162). All results reflect analysis of data from these 327 infants. See Figure C1, Study Diagram.

The infants in the two groups were similar in all demographic and biometric characteristics, with the exception of Cesarean delivery, which occurred with 54% of births in the PCV group and 40% of births in the Hib group (p = 0.01). See Table C1, Participant Characteristics.

Data collection was complete for 99% of weeks in the PCV group and 98% of weeks in the Hib group. 5 infants (3%) in each group were lost to follow up between 10 and 24 weeks. Interviews were conducted either over the phone (48%), during a home visit (43%), or while at a clinic visit (9%).

When one or more interviews were missed, data for two or more weeks were collected at the next interview. The percentage of interviews conducted one or more weeks late was similar between the two groups. Average lateness per interview was also similar.

**Effectiveness**

There were 5.5% and 6.2% of infants in each group who had ≥ 1 ASOM episode in the PCV and Hib groups, respectively (p = 0.79). ASOM episodes per 100 child-months were 1.95 for the PCV group and 2.18 for the Hib group (p = 0.80). Mean ASOM episode duration was 4.1 days per episode for the PCV group compared to 12.2 days per episode for the Hib group (p = 0.0048). The difference in mean episode durations was 8.1 days (95% CI, 1.5–14.7), with a reduction in episode duration of 66%. Overall, the infants in the PCV group experienced 70% fewer days of ASOM per 100 child months compared to infants in the Hib group (6.1 vs. 26.7, p < 0.0001). See Table C2.

The incidence of ASOM in the whole study population (n=327) using data collected from birth to 24 weeks was 0.074 episodes per 6 child months. Among the 19 infants who had at least one ASOM episode, 16 were males and 3 were females (Fischer Exact two-tailed p = 0.0087).
Among the 9 infants in the PCV group with ASOM, 1 (11%) was female (Fischer Exact two-tailed p = 0.039). Among the 10 infants in the Hib group with ASOM, 2 (20%) were female (Fischer Exact two-tailed p = 0.19).

Two infants in the Hib group accounted for 4 of the 12 ASOM episodes, 15 of the 31 weekly reports of ASOM, and 80.5 of the 147 days of ASOM. (See Figure C2, rows 8 and 10.) None of these 4 episodes were treated with antibiotics during the first week of the episode. 3 of the episodes were treated with antibiotics on the second week. The other was treated on the fourth week of the episode. Both of the infants were males born at 40 weeks gestation. One of the infants weighed 3.4kg (62nd percentile) at birth and 6.1kg (1st percentile) at 24 weeks. No weights were recorded for the other infant.

Discussion

This analysis suggests that the administration of PCV at 6, 10, and 14 weeks may substantially decrease the duration of ASOM episodes in young infants. The magnitude of the PCV’s effect is evidenced by the large (70%), statistically significant reduction in prevalence, despite a relatively small number of episodes (11 in the PCV group and 12 in the Hib group). Since PCV appears to reduce the duration of ASOM episodes, there is a possibility that PCV may also decrease the progression of ASOM to CSOM, which could lead to a significant reduction in the morbidity and mortality due to otitis media, which occurs predominantly due to CSOM. Kaplan et al. demonstrated this relationship in a study in Alaska in the 1960’s. They found that children with a history of otitis media as infants were twice as likely to have hearing loss at 10 years of age. They also showed that having ASOM episodes of longer duration may predispose children to developing CSOM and its complications.

The strengths of this analysis include its blinded, randomized design and its prospective data collection with frequent surveillance through weekly interviews. Randomization was effective and achieved groups with similar baseline characteristics. The study had a high level of data completeness and a low percentage of infants lost to follow up in both groups.

Although the study was not placebo-controlled, it was essentially comparison-controlled using the Hib vaccine. The Hib vaccine is not effective against the nontypeable strains of Haemophilus influenzae which cause 12% to 23% of otitis media episodes. Hib is a causative agent in otitis media on rare occasions (0.4% of cases), so the Hib vaccine is unlikely to have had a significant effect on ASOM in infants who received it. Furthermore, if the Hib vaccine
provided protection against ASOM, it would lead to an underestimation of the effect of the PCV on ASOM.

The study was limited by the lack of bacteriologic and clinical exam data. However, since diagnosis of ASOM was based on parental report of ear drainage, only severe cases were detected. Among these severe and presumably more clinically relevant cases, the efficacy of the PCV for reducing ASOM episode duration was clear.

Noticing ear drainage is a fairly simple task, but using parental report of otorrhea for detection of ASOM may have resulted in both under-diagnosis, when parents did not notice drainage, and over-diagnosis, when parents noted cerumenous discharge that was mistaken for otorrhea. Even though parental report may have led to inaccuracy in detection of ASOM, it should not have led to any differential bias.

4.9% of data was from late interviews, which involved recall of information from greater than 7 days earlier. Since the average lateness of the interviews was similar in both groups, this would not cause a differential bias. Because none of the reports of ASOM were from late interviews, underestimation of ASOM episodes would be possible, but not overestimation.

Many previous studies have confirmed the safety of the vaccines given to both groups of infants. As a result, there is no reason to expect any differences in hospitalizations or adverse events between the two groups.

The sex differences in the incidence of ASOM in our analysis are striking. There are multiple plausible explanations for this difference. One likely significant contributor is a parental bias of increased attention to the symptoms of male infants compared to female infants. Hossain et al. demonstrated such a bias in the nearby rural area of Matlab, Bangladesh. However, the difference found in our analysis could reflect a true difference in disease. Roy et al. found that 63% (236/375) of episodes of otitis media in the first two years of life occurred in males. Jensen et al. found that in Greenland boys and girls had equal risk of developing CSOM, but that girls had higher muc higher rates of spontaneous healing, resulting in boys having increased rates of CSOM persistence.

For the first 24 weeks of life, this analysis found an incidence of 0.074 episodes of ASOM per 6 child months. Roy et al. identified approximately 0.25 episodes of acute otitis media per 6 child months during the first 6 months of life. This discrepancy is most likely due to our study population being urban and the Roy et al. study population being rural, as other studies
have documented higher percentages of otitis media in rural settings.\textsuperscript{48-50} The incidence from Roy et al. is based on 61 episodes, an uncertain percentage of which are acute otitis media without otorrhea (Overall the study identified 375 episodes between birth and 24 months, 53 (14\%) of which were otitis media without otorrhea. Furthermore, their measurement of otitis media was likely more sensitive since they conducted interviews every 4 days instead of every 7.

The findings of this analysis are unique and would need to be replicated before a definitive conclusion can be made. In this analysis, PCV caused a large and statistically significant reduction in ASOM and CSOM. Worldwide there is substantial morbidity and mortality caused by ASOM and CSOM. This effect certainly merits further investigation, since confirmation of it would suggest that PCV may have significant beneficial effects in addition to its already recognized ability to decrease invasive pneumococcal disease. To follow up on this analysis, plans are being made to assess the hearing of the original participants of this study to measure the effects of PCV on long-term ASOM and CSOM-related morbidity.
Figure C1. Study Diagram

823 pregnant women screened

483 were not enrolled

340 Infants enrolled and randomized (before birth)

171 infants assigned to receive PCV
169 infants assigned to receive Hib vaccine
6 infants lost to follow up before intervention
7 infants lost to follow up before intervention

165 infants with data available for analysis
Data collected for 99% of weeks
81% had 2 or more doses of PCV
5 infants lost to follow up between 10 and 24 weeks

162 infants with data available for analysis
Data collected for 98% of weeks
80% received 2 or more doses of Hib vaccine
5 infants lost to follow up between 10 and 24 weeks

<table>
<thead>
<tr>
<th>Table C1: Patient Characteristics</th>
<th>Experimental Group (PCV) n = 165</th>
<th>Comparison Group (Hib) n = 162</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age (yr)</td>
<td>25.18</td>
<td>24.93</td>
<td>0.60</td>
</tr>
<tr>
<td>Parity</td>
<td>1.12</td>
<td>1.14</td>
<td>0.88</td>
</tr>
<tr>
<td>Maternal inactivated influenza vaccine (%)</td>
<td>49.70</td>
<td>50.62</td>
<td>0.87</td>
</tr>
<tr>
<td>Maternal Pneumococcal polysaccharide vaccine (%)</td>
<td>50.30</td>
<td>49.38</td>
<td>0.87</td>
</tr>
<tr>
<td>Maternal height (cm)</td>
<td>152.80</td>
<td>152.70</td>
<td>0.94</td>
</tr>
<tr>
<td>Maternal education (yr)</td>
<td>11.27</td>
<td>10.96</td>
<td>0.43</td>
</tr>
<tr>
<td>Family owns house (%)</td>
<td>34.55</td>
<td>30.25</td>
<td>0.41</td>
</tr>
<tr>
<td>Rooms in house (Number)</td>
<td>3.76</td>
<td>3.53</td>
<td>0.27</td>
</tr>
<tr>
<td>Smoker in family (%)</td>
<td>46.06</td>
<td>39.51</td>
<td>0.23</td>
</tr>
<tr>
<td>Gestational age at birth (wk)</td>
<td>39.43</td>
<td>39.58</td>
<td>0.44</td>
</tr>
<tr>
<td>Infants born in a hospital or clinic (%)</td>
<td>94.55</td>
<td>89.51</td>
<td>0.09</td>
</tr>
<tr>
<td>Infants with Cesarean delivery (%)</td>
<td>53.94</td>
<td>40.12</td>
<td><strong>0.01</strong>*</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.22</td>
<td>3.19</td>
<td>0.80</td>
</tr>
<tr>
<td>Weight at 6 wks (before first vaccination)</td>
<td>4.36</td>
<td>4.25</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean Apgar score at 1 minute</td>
<td>8.35</td>
<td>8.32</td>
<td>0.98</td>
</tr>
<tr>
<td>and 5 minutes</td>
<td>9.47</td>
<td>9.36</td>
<td>0.92</td>
</tr>
<tr>
<td>Sex of infant female (%)</td>
<td>45.45</td>
<td>41.36</td>
<td>0.45</td>
</tr>
<tr>
<td>Duration of exclusive breast-feeding (wk)</td>
<td>15.63</td>
<td>15.50</td>
<td>0.90</td>
</tr>
</tbody>
</table>

*Means were compared using the Student’s t-test. Proportions were compared using Fisher’s exact test.
‡ The rate of cesarean delivery was typical for the population of patients at the study centers.
§ The Apgar scores are 0 to 10. Scores above 7 indicate that the baby’s condition is good to excellent.
Table C2. Measurements of ASOM and CSOM for the PCV and Hib Vaccine Groups

<table>
<thead>
<tr>
<th></th>
<th>PCV Group</th>
<th>Hib Vaccine Group</th>
<th>P Value</th>
<th>Relative Rate or Difference in Means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>165</td>
<td>162</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant months observed</td>
<td>564.30</td>
<td>551.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants with one or more episodes of ASOM</td>
<td>9 (5.5%)</td>
<td>10 (6.2%)</td>
<td>0.7874</td>
<td></td>
</tr>
<tr>
<td>Episodes of ASOM</td>
<td>11</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes of ASOM per 100 child months</td>
<td>1.95</td>
<td>2.18</td>
<td>0.7956</td>
<td></td>
</tr>
<tr>
<td>Episodes of CSOM (duration &gt; 2 weeks)</td>
<td>0</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes of CSOM per 100 child months</td>
<td>0</td>
<td>0.73</td>
<td>0.0597</td>
<td></td>
</tr>
<tr>
<td>Total days of ASOM per group</td>
<td>45.5</td>
<td>147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean duration of ASOM episode*</td>
<td>4.14</td>
<td>12.25</td>
<td>0.0048*</td>
<td>8.11 (1.53, 14.70) †</td>
</tr>
<tr>
<td>Days of ASOM per 100 child months</td>
<td>8.06</td>
<td>26.66</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Days of ASOM per infant with ASOM</td>
<td>5.06</td>
<td>14.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in days at time of first report of ASOM</td>
<td>114.33</td>
<td>125.30</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Weekly reports of ASOM</td>
<td>13</td>
<td>31</td>
<td></td>
<td>0.41 (0.21, 0.78) §</td>
</tr>
</tbody>
</table>

*Wilcoxon test used due to small sample size
† Difference in Means
§ Relative Rate
Figure C2: Weeks with reported ASOM, 10-24 weeks of age, by infant vaccine

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