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Katharina L. van Santen Date

Efficacy (Effectiveness) of Pneumococcal Conjugate Vaccine in Infants by Maternal Influenza Vaccination

By

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B.S., University of Alabama in Huntsville, 2010

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An abstract of

a thesis submitted to the Faculty of the
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Abstract

Efficacy (Effectiveness) of Pneumococcal Conjugate Vaccine in Infants by Maternal Influenza Vaccination

By Katharina L. van Santen

BACKGROUND: Influenza virus can predispose patients to secondary pneumococcal infections, potentially resulting in increased otitis media or other pneumococcal-related outcomes. Children are at greatest risk for pneumococcal infection in the first year of life. However, they are not considered fully protected by PCV until the third dose, adminstered at 6 months of age, and there is currently no influenza vaccine licensed for infants under 6 months of age. Maternal influenza vaccination during pregnancy can protect infants from respiratory diease during this time of increased susceptibility.

METHODS: We conducted a retrospective cohort study of 5,525 mother-infant pairs enrolled in an MCO, with infants born during the influenza season. Exposure was assessed for receipt of maternal influenza vaccine, infant pneumococcal vaccine (PCV7), and the combination of vaccines. Outcomes of interest were acute otitis media (AOM) and medically attended acute respiratory infection (MAARI) in the first year of life. We estimated the incidence of illness, incidence rate ratios, and vaccine effectiveness based off of the ratio of incidence rate ratios between the pre-influenza circulation period and the period of at least local influenza circulation.

RESULTS: Initial AOM and MAARI rate estimates were higher in infants born during pre-influenza circulation periods, compared to periods of influenza circulation, and were higher among infants who received any combination of vaccines compared to those who received no vaccine in both periods. When controlling for period of birth using the ratio of ratios method, lower rates of AOM and MAARI were observed for infants with any vaccine exposure, compared to infants who received neither vaccine. Relative to infants who were exposed to neither vaccine, the effectiveness of combined pneumococcal vaccination and maternal influenza vaccination was 35.7% (95% confidence interval [CI]: -3.3, 60) $_{\text{and}}$ 13.9% (95% CI: -24.7, 40.6)for infants who received only PCV7.

CONCLUSIONS: The combination of maternal influenza vaccination and infant pneumococcal vaccination seems to confer more protection from acute otitis media infections in the first year of life than infant pneumococcal infection alone.

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Thank you to my parents, who first taught me to love all things science and statistics. Together we have come to realize that although times may get difficult, you will always end up back on two feet.

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BACKGROUND

Global and U.S. Burden of Pneumococcal Diseases

Streptococcus pneumoniae are alpha-hemolytic, gram positive, lancet-shaped cocci, which can form chains or diplococci pairs.[1] *S. pneumoniae* are coated in a polysaccharide capsule, which is an essential virulence factor for the bacterium. There are 90 identified serotypes arising from differences in this polysaccharide capsule.[2] Humans are the host of choice for *S. pneumoniae*, which colonizes the nasal cavity and respiratory tract. Colonization can occur without clinical disease, but those who are colonized often serve as carriers of the bacterium, which can lead to transmission and infection in others. When the bacterium moves past the nasal cavity, disease can occur. *S. pneumoniae* disproportionally affects the young and the old, and has varying degrees of disease manifestation in humans. Serious disease such as invasive pneumococcal disease (IPD), sepsis, and meningitis can occur, as well as lesser infections such as pneumonia, otitis media, and sinusitis.[3]

IPD is one of the severest forms of *S. pneumoniae* infection. 12 Internationally, more than 80% of IPD cases occurring in all age groups are associated with approximately 20 of the 90 serotypes of *S. pneumoniae*. The 13 most common serotypes cause at least 70–75% of cases of IPD in children.[2] Pneumonia was one of the six leading causes of death in children under five years of age from 2000-2003 (prior to large scale vaccination), accounting for 19% of the 10.6 million deaths a year worldwide.[4] *S. pneumoniae* is the most common bacterial cause of pneumonia, bacteremia, sinusitis, and otitis media.[5,6]

In the United States, young children are at the highest risk for a *S. pneumoniae* infection.[3,5,7,8] Prior to widespread vaccination, the incidence of IPD in children less than one year of age was 165 cases per 100,000 children. The peak incidence of IPD was 235 cases per 100,000 children

in children age 6-11 months.[5] Children less than 1 year of age also had the highest incidence of pneumococcal meningitis, 10 cases per 100,000 children.[5] *S. pneumoniae* is the most common bacterial cause of community-acquired pneumonia, sinusitis, and acute otitis media among young children.[5,8] The highest rate of otitis media infections are in children between 6 and 18 months of age. Approximately half of all infants experience their first episode of otitis media by 6 months of age. Otitis media is the most common reason for a physician office visit and the most common reason for an antibiotic prescription in young children.[6,8] One study estimated the rate of office visits to be 2,173 per 1,000 person-years and the rate of antibiotic prescriptions given for otitis media to be 1,244 per 1,000 person years, prior to introduction of the introduction of a pneumococcal vaccine for young children.[8]

Pneumococcal Conjugate Vaccine

The pneumococcal conjugate vaccine was first licensed in the United States in 2000 as PCV7, a 7-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV7; Prevnar, Wyeth). It was recommended for all children aged 2-23 months and at-risk (immunocompromised) children up to 59 months. In 2007 the recommendation was revised to include all children 2-59 months. Included in this vaccine were the serotypes 14, 6B, 19F, 18C, 23F, 4, and 9V, chosen because they made up 80% of all types of pneumococcal infections in children under 6 years of age, and 50% of pneumococcal infections 6 years of age or older.[2,5] The serotypes included in PCV7 were also those that were most frequently found to be antimicrobial resistant.[5] Disease caused by antimicrobial resistant pneumococcal serotypes can often be more severe and last longer because it is more difficult to treat.

PCV7 induces a T-cell dependent immune response, which creates protective immunity and immunological memory, even in infants and in many immunodeficient patients. The vaccine protects against both systemic and mucosal infection.[2] In those vaccinated, PCV7 also prevents

nasopharyngeal colonization with PCV7 serotypes. This rapid reduction of colonization led to a reduction of transmission and colonization in older children and adults who were not vaccinated, but who were protected through indirect effects and heart immunity.[2,9,10] Within two years of the start of vaccination, levels of pneumococcal disease in young children declined and reached a steady state. Within six years of the start of vaccination levels of pneumococcal disease in the rest of the population declined and reached a steady state.

Despite the dramatic decline in colonization and disease in all age groups, overall rates of disease did not decrease as much as hoped due in large part to serotype replacement of nasopharyngeal colonization (and disease) with non-PCV7 serotypes.[11] Serotype 19A, which was not included in the PCV7 vaccine, has increased in prevalence of carriage and as a cause of disease since licensure of the vaccine. A 2007 Active Bacterial Core surveillance (ABCs) study in children less than five years of age showed that the rate of IPD caused by serotype 19A was 2.6 cases per 100,000 prior to use of PCV7. In 2007, this rate increased 324% to 11.1 cases per 100,000.[12] There were 427 cases of IPD in children less than five years of age, 274 (64%) were caused by serotypes that were later included in the 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13). Of these 274 cases, 260 (95%) were caused by three of the six additional serotypes (3, 7F, and 19A) that are not included in PCV7.[12,13] In February 2010, to combat serotype replacement and further reduce pneumococcal disease rates, a new 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13 [Prevnar 13, Pfizer Inc.]), was licensed in the U.S. to replace PCV7. PCV13 contains all serotypes in PCV7, plus six additional serotypes: 1, 3, 5, 6A, 7F, and 19A. The vaccination recommendations were also expanded to a recommended age range to 6 weeks-71 months.[13] It is hoped that the PCV13 vaccine with further reduce the burden of IPD, other pneumococcal infections, and colonization.

In initial efficacy trials, the PCV7 was indicated to be effective at preventing invasive pneumococcal disease and have a significant impact on otitis media.[14] Serotypes included in

PCV7 cover 65–80% of serotypes associated with invasive pneumococcal disease among young children in western industrialized countries.[2] In children who completed a three dose sequence of PCV vaccine, otitis media visits were reduced by 7.8% (95% Confidence Interval [CI]: 5.4, 10.1). Visits in children under one year of age were reduced by 10.1% (95% CI: 5.1, 11.1).[15]

Since PCV7 is relatively new, there have only been a few effectiveness studies completed on PCV7. Some studies have been done abroad, but are not easily extrapolated to the United States due to different dosing schedules. Overall, studies have focused on IPD and all-cause pneumonia rather than looking at Otitis Media or MAARI (as is the focus of our study). They have found that in the United States IPD has decreased by 77% in children less than 5 years of age, and there has been a 39% decrease in hospital admissions for pneumonia in children under 2 years of age, five years after introduction of PCV.[10,11] Our study seeks to fill the knowledge gap of effectiveness of PCV for otitis media and MAARI.

PCV7 coverage has steadily increased since the vaccine was first licensed for use in the United States in 2000.[5] In 2003, when data were collected on the first cohort of able to receive PCV7 at age-appropriate intervals, coverage for three doses of PCV7 was 57.1% (95% CI: 57.0 , 58.2) in children 13 months of age.[16] In 2005, just two years later, coverage for three doses of PCV7 was 71.4% (95% CI: 70.2 , 72.6) in children 13 months of age.[17] In 2010 coverage for three doses of PCV13 was 88.2 (95% CI: 87.9 , 89.1) in children 13 months of age. Coverage varies by location. In 2010, for 3 dose coverage in the 13-month age group, the lowest coverage was in the U.S. Virgin Islands with 68.3% (95% CI: 60.9, 75.7), and the lowest coverage in the 48 contiguous states was in Montana with 78.3% (95% CI: 72.3 , 84.3). The highest coverage was in New Hampshire with 97.6% (95% CI: 95.9, 99.3) coverage.[18] The high coverage rates found in the United States are, however, not a global phenomenon.

Data suggest that, in developing countries, the incidence of invasive pneumococcal disease in children less than 5 years of age is several times higher than it is in industrialized countries such as the United States. The World Health Organization (WHO) recommends including PCV in national immunization programs (i.e. routine vaccination of all young children with PCV), particularly in countries where all-cause mortality among children less than 5 years of age is more than 50 per 1,000 live births, or where more than 50,000 children die annually from any cause. In 2008, 90 of the 193 WHO member states worldwide had PCV7 vaccine licensed. However, only 27 countries had widespread use of PCV7 vaccination as part of their national immunization programs. No low-income or lower-middle income countries had large scale PCV7 vaccination. These low-income countries account for more than 97% of pneumonia cases in children less than 5 years of age, and would therefore benefit the most from introduction of PCV. The burden of pneumococcal disease is also substantially higher among HIV infected individuals. Therefore, since PCV7 has been shown to be safe and efficacious in HIV infected children, PCV7 is also recommended for countries where HIV is a significant cause of mortality.[2,11] The Global Alliance for Vaccines and Immunisations (GAVI) began funding for PCV in 2010, with a goal of bringing PCV to 35 new countries by 2015.[19]

Maternal Influenza Vaccination and Pneumococcal Conjugate Vaccine

Previous research has shown that influenza virus can predispose patients to secondary infections, especially otitis media and other pneumococcal outcomes, although the exact mechanism is unclear.[7,20-22] No influenza vaccine is licensed for infants under 6 months of age, and antivirals that can be used to treat influenza are not licensed for infants under 1 year of age.[23,24] Children are at greatest risk for pneumococcal infection in the first year of life, and are not considered fully protected by PCV until the third dose adminstered at 6 months of age.[5,14,25]

Maternal influenza vaccination fills an important gap in protection from pneumocccal disease in the first months of life.

The influenza vaccine has been administered to pregnant women in the United States since 1957.[26,27] Maternal influenza vaccination has been shown to provide protection to infants through maternal antibody transfer.[28] Active trans-placental transport of immunoglobulin G produces higher levels of antibodies in the umbilical cord than in maternal serum.[29] Since 1997, influenza vaccination with trivalent inactivated vaccine (TIV) has been recommended by the Centers for Disease Control and Prevention (CDC) for all pregnant women in their second or third trimester during influenza season, and during all trimesters for certain chronic medical conditions.[30,31] Since 2004, the Advisory Committee on Immunization Practices and the American College of Obstetricians and Gynecologists (ACOG) have recommended TIV for all women who are pregnant during influenza season, regardless of trimester.[32,33] As of 2010, seasonal influenza vaccination has been recommended for all adults in the U.S.[34] Despite these recommendations, maternal TIV coverage has been low in the United States. Prior to the 2009 H1N1 pandemic, the TIV vaccination rate among pregnant women was approximately 15%. During the H1N1 pandemic, pregnant women were included in the initial target groups to receive the inactivated 2009 H1N1 pandemic vaccine. The CDC and ACOG worked together to increase awareness that pregnant women were at increased risk for severe illness from H1N1 influenza and were recommended for vaccination to protect themselves and their infants. Because of this, vaccination coverage in 2009-2010 increased to approximately 50% and stayed that way through the 2010-2011 influenza season.[32] However, vaccination levels are still below the Healthy People 2020 target of 80% influenza vaccination coverage for pregnant women.[35] Barriers to vaccination by health care providers include lack of infrastructure for vaccine storage, lack of training for nurses to administer vaccines, and concern about safety and related lawsuits for vaccinating first trimester women.[36]

Bangladesh Study

The concept for study was largely influenced by unpublished secondary data from the Bangladesh trial of the effect of maternal influenza vaccination on infant outcomes.[37] In the Bangladesh trial, women were randomized to receive either a seasonal influenza vaccine or the PPV23, 23-valent pneumococcal polysaccharide vaccine (used in adults rather instead of the PCV7 vaccine). Their infants were further randomized to receive either the PCV7 vaccine or the *Haemophilus influenzae* type b (Hib) vaccine. Infants in all groups were monitored for respiratory illness. Those infants whose mother's received the influenza vaccine and who themselves received either PCV7 or Hib vaccines had much lower incidence of respiratory illness and pneumococcal colonization than did the children whose mothers had received the PPV23 vaccine.

This study aims to build on in information gained from the Bangladesh trial to determine if maternal influenza vaccination and infant pneumococcal conjugate vaccine in the United States have a synergistic protective effect in protecting young infants from otitis media and medically attended acute respiratory infection.

MANUSCRIPT

Introduction

Streptococcus pneumoniae is the leading cause of bacterial pneumonia, bacteremia, sinusitis, and otitis media in the United States and globally. In the United States, young children are at the highest risk for a *S. pneumoniae* infection.[3,5,7,8] Prior to widespread vaccination, pneumonia was one of the six leading causes of death in children under five years of age, accounting for 19% of all childhood deaths.[4] Otitis media is the most common reason for physician office visits and antibiotic prescriptions in young children.[6,8] Previous research has shown that influenza virus can predispose patients to secondary infections, especially otitis media and other outcomes associated with pneumococcal disease, although the exact mechanism is unclear.[7,20-22]

Pneumococcal conjugate vaccine (PCV) has been recommended for routine use in children in the United States since 2000, with doses given at 2,4,6 and 12-15 months of age. Children are at greatest risk for pneumococcal infection in the first year of life, and are not considered fully protected by PCV until two weeks after the third dose adminstered at 6 months of age.[5,14,25] In 2002, influenza vaccination was recommended for children 6-23 months of age, with age ranges expanded several time until universal vaccination recommendations in 2010.[38-41] Both vaccines leave children only partially protected in their first six months of life. Maternal influenza vaccination can protect infants from respiratory infections in their first months of lifethrough maternal antibody transfer.[28] Pregnant women have been recommended to receive trivalent inactivated vaccine (TIV) since 1997.[30,31]

The efficacy of PCV in preventing invasive pneumococcal disease, pneumonia, and otitis media has been well established.[8,10,15,42,43] Additionally, maternal influenza vaccination for the protection of mother and infant from respiratory and other outcomes has been well studied.[26-

[29,32,36,37,44-49] However, in the United States, there have been no published studies examining the combined effect of maternal TIV and infant PCV vaccination. We sought to address this research gap by evaluating the combined effectiveness of maternal TIV and infant PCV on medically attended acute respiratory infection (MAARI) and acute otitis media (AOM) in children less than one year of age.

Methods

We conducted a retrospective cohort study using longitudinal electronic data from Kaiser Permanente Georgia, a large managed care organization (MCO) in the metropolitan Atlanta area. The primary exposures were maternal receipt of trivalent influenza vaccine (TIV) during pregnancy and child pneumococcal conjugate vaccine (PCV) receipt through the first year of life. Exposures were assessed for children born in the MCO during periods of pre-influenza circulation, and at least local influenza virus circulation from October 1, 2002 and December 31, 2009. Influenza circulation information was not available prior to the 2002-2003 influenza season; earlier births were excluded from this study.[50] The outcomes of interest were medically attended acute respiratory infection (MAARI) and acute otitis media (AOM).

We identified infants born between October 1, 2000 and December 31, 2009, in periods of pre-influenza virus circulation or periods of at least local influenza circulation (Table 1). Pre-influenza periods were defined as any birth after the beginning of the putative influenza season, October 1, but prior to at least local influenza virus activity. Births during the circulating influenza period were any birth during the putative influenza period where there was at least local influenza virus spread. Births during H1N1 activity that did not occur during the putative influenza season, October-May, were also included in the analysis.

Infants included in the study are those that were enrolled in the MCO within 30 days of birth, and continuously enrolled for at least 60 days, and for whom record linkages to mothers enrolled in the MCO could be identified. Mother-infant pairs were excluded if mothers were not continuously enrolled for 20 weeks prior to birth, to allow capture of maternal TIV receipt. Follow-up for infants ended when the infant reached their first birthday, received their fourth valid dose of PCV7 vaccine, or were disenrolled from the MCO.

Infant PCV vaccination status was assessed at exit from the study for each infant, and determined to be up to date, not up to date, or no doses given. Those who were not up to date were excluded because of lack of generalizability. Infants were considered up to date if they had received the appropriate number of doses at the end of study enrollment disenrollment from the study, allowing for a 2-week window to account for late doses. The fourth PCV dose was not considered in this study since it is recommended to be administered after the one year of age. Maternal TIV vaccination 40 weeks prior to infant birth was assessed. Women without a history of influenza vaccination during this time period were considered negative for TIV vaccination, while those with a record of vaccination were considered positive. Based on this dual exposure, four vaccination groups were considered in the study: PCV-TIV-, PCV-TIV+, PCV+TIV- and PCV+TIV+, where PCV+ indicates up to date PCV vaccination status and PCV- indicates no doses of PCV were received. PCV-TIV- served as the referent group.

Outcomes were identified based on ICD-9 codes for AOM and MAARI. Power calculations for a sample size of 5,000 estimated greater than 90% power to detect rate ratios less than 0.75 for AOM and MAARI in all vaccination groups.

Invasive Pneumococcal Disease was also considered as a possible outcome, but was omitted due to low study power. Unique episodes of AOM or MAARI were episodes that occurred more than 14 days after the previous episode.

We evaluated the association between vaccination group and the number of AOM and MAARI cases per infant during the study period using Poisson regression. We calculated IRRs for infants born during pre-influenza periods and periods of influenza circulation, for each exposure group, relative to PCV-TIV-. To account for unmeasured confounding and differences in vaccination groups due to healthy vaccinee bias.[51,52] We controlled for these differences using a ratio-of-ratios approach. Ratios of IRRs (R-IRR) were calculated with outcomes for infants born prior to influenza circulation considered to occur during the control period, and outcomes for infants born during the circulating influenza period considered to occur during the exposure period. Vaccine effectiveness for each vaccination combination was calculated defined as 1— R-IRR. This analysis was done for the full cohort and for a reduced cohort of births excluding births during periods of H1N1 circulation. A further sub analysis was completed using only births during the period of H1N1 circulation, with an average of IRRs for previous pre-influenza circulation periods used as the control period, as the circulation of H1N1 virus did not follow typical patterns increases and decreases in influenza activity as seen during seasonal influenza epidemics.

All analyses were adjusted for available covariates. We considered several covariates selected a priori (i.e. mother's race, mother's age, mother's influenza vaccination status in previous years, multiple birth, first birth in MCO, infant's race, infant's sex, infant's number of well visits in study period, infant's number of non-study outcome related sick visits in study period, and infant's influenza vaccination status (after 6 months of age). Mother's race and infant's race were imputed using the Geographically Enriched Member Sociodemographics (GEMS) database, where members with race probabilities greater than 80% were considered to be of that race.[53-56] Additional covariates that could not be considered due to inadequate data included type of birth (Cesarean section vs. vaginal birth), low birth weight, and underlying conditions for both the mother and infant. Covariates identified a priori that were retained as covariates were: mother's

race, infant's sex, infant's well visits in the study period, and infant's non-study outcome related sick visits in the study period were retained as confounders.

All statistical analyses were conducted using SAS version 9.2 (Cary, NC), at a two-tailed significance level of α=0.05. The study was reviewed and approved by the Kaiser Permanente Georgia Institutional Review Board.

Results

We identified 13,657 infants enrolled in the MCO with births during the pre-influenza period or circulating influenza period from October 1, 2002 to December 31, 2009, who were enrolled within 30 days of birth. Of these 2,224 were excluded because their first enrollment was not longer than 60 days. Additionally 1,525 infants were excluded because they lacked a valid link to their mother, and 6,018 were excluded because their mothers were not enrolled for at least 20 weeks prior to birth. The cohort was further restricted by excluding 413 infants from the study who had received some doses of PCV, but were not up to date at exit from the study. This yielded a study population of 5,525 mother-infant pairs eligible for the study. For the analysis that excluded births during H1N1 circulation, this was further restricted to 4,797 births when births during H1N1 influenza circulation were excluded (Figure 1).

In the full influenza season cohort of 5,525 mother-infant pairs, 1,788 (32%) mothers received influenza vaccine during their pregnancy. The coverage among mothers who met the inclusion criteria increased from 8% in the 2002-03 influenza season to 63% during the 2009-10 influenza season. Overall, 4,505 (82%) infants were up to date for PCV vaccination at exit from the study. PCV up to date vaccination coverage for the infants who met the inclusion criteria ranged from 71% in the 2002-03 influenza season to 93% in the 2004-05 influenza season.

There were 2,771 cases of AOM reported after 2 months of age, with cases occurring in 1,996 (36%) infants; among infants who had at least one case, there were an average of 1.4 (range:1-7) cases per infant. There were 4,121 cases of MAARI reported, with cases occurring in 2,549 (46%) infants; among infants who had at least one case, there were an average of 1.6 cases (range: 1-7) per infant (Table 1). Composite mother-infant vaccination status was classified into four exposure groups based on TIV and PCV vaccination status: 1,673 (30%) were PCV+TIV+, 2,835(51%) were PCV+TIV-, 115 (2%) were PCV-TIV+, and 902 (16%) made up our PCV-TIV- referent group. Enrollment time varied substantially by group; of the infants who received PCV 79% stayed enrolled through 1 year of age, while only 42% of infants who did not receive PCV stayed enrolled a full year. Infants who were up to date for PCV had on average one more well child visit in the study period than their counterparts who did not receive PCV. Infants in the PCV-TIV- referent group had the lowest number of non-outcome sick visits and well visits in the cohort (Table 2).

Adjusted IRRs for AOM for both pre-influenza period and influenza circulating period births were elevated relative to the PCV-TIV- referent group. Adjusted IRRs for MAARI for pre-influenza period births were also elevated relative to the PCV-TIV- referent group. IRRs for pre-influenza period births were higher than for circulating influenza period births for both AOM and MAARI. This is attributed to healthy vaccine bias, as individuals who are more likely to seek vaccines may be more likely to seek other healthcare. Significant reductions in R-IRRs for AOM and MAARI were identified for all vaccine groups, relative to the PCV-TIV- referent group. Mother-infant pairs who received both TIV and PCV had a 36% reduction in cases of AOM, and an 18% reduction in MAARI cases compared to mother-infant pairs who received neither vaccine. This is a marked increase from mother-infant pairs who only received TIV, who had a 14% reduction in cases of AOM, and a 4% reduction in MAARI cases compared to mother-infant pairs who received neither vaccine (Table 4). The PCV-TIV+ group had the lowest R-IRR for

MAARI, showing a 36% reduction in MAARI cases. However, this group only made up 2% of our population. H1N1 only analysis showed similar results to the analysis of all influenza seasons (Supplement table 1).

Discussion

This is the first study to evaluate the joint effect of maternal TIV and infant PCV on preventing AOM and MAARI in infants in the United States. Our findings show a decrease in AOM and MAARI in mother-infant pairs who received either or both vaccines, compared to those who received neither vaccine. An interaction of maternal TIV and infant PCV immunization appears to be shown: PCV vaccination alone reduced cases of AOM after two months of age by 14%, while the combination of maternal TIV vaccination and infant PCV vaccination reduced cases of AOM by 36%.

MAARI visits were reduced in all vaccination groups, compared to those who received no vaccine; however we did not observe the same level of biological synergism as observe with the AOM outcome. This could be due to our broad definition of MAARI, which was not limited to influenza or pneumococcal disease or due to absence of interaction.

To reduce confounding by indication, outcomes and person-time prior to 2 months of age were omitted from the study since these would occur prior to receipt of PCV. We used a ratio-of-ratios approach to further account for differences in vaccination exposure groups due to unmeasured confounding and the healthy vacinee effect.[51,52]

Strengths of the study come from the retrospective cohort study design within an MCO. The likelihood of exposure misclassification is minimal, since most pregnant women are vaccinated in their gynecologist's office (51%), with another 15% receiving influenza vaccine at their family physician's office.[32] Childhood immunizations are unlikely to occur outside of the MCO. The

majority of our cohort had the opportunity to receive PCV: on average infants in the study were enrolled 11 months, and 72% of the cohort was enrolled for their first year of life. This long enrollment time also ensured that we captured the majority of the cases of AOM and MAARI in the first year of life.

Because of the retrospective nature of this study, we do not have any information beyond enrollment and physician visits on reasons why mothers did not receive TIV or why infants did not receive PCV. Our outcome definitions, especially for MAARI, were broad and did not involve any diagnostic testing.

We showed an effect of maternal TIV and infant PCV on both AOM and MAARI. There was a synergistic effect of TIV and PCV in the reduction of AOM. Uptake of infant PCV has been quick, already over 50% by 2003, and up to 88% in 2010 in children 13 months of age.[16,18] Maternal influenza coverage has increased steadily in the past ten years, but only 50% of pregnant women are receiving vaccine, well below the Healthy People 2020 target of 80% influenza vaccination coverage for pregnant women.[35] In order to make the most of this combined effect of TIV and PCV, TIV coverage must increase.

Disclaimer: This thesis is an initial analysis as part of a larger project, final results may vary.

TABLES AND FIGURES

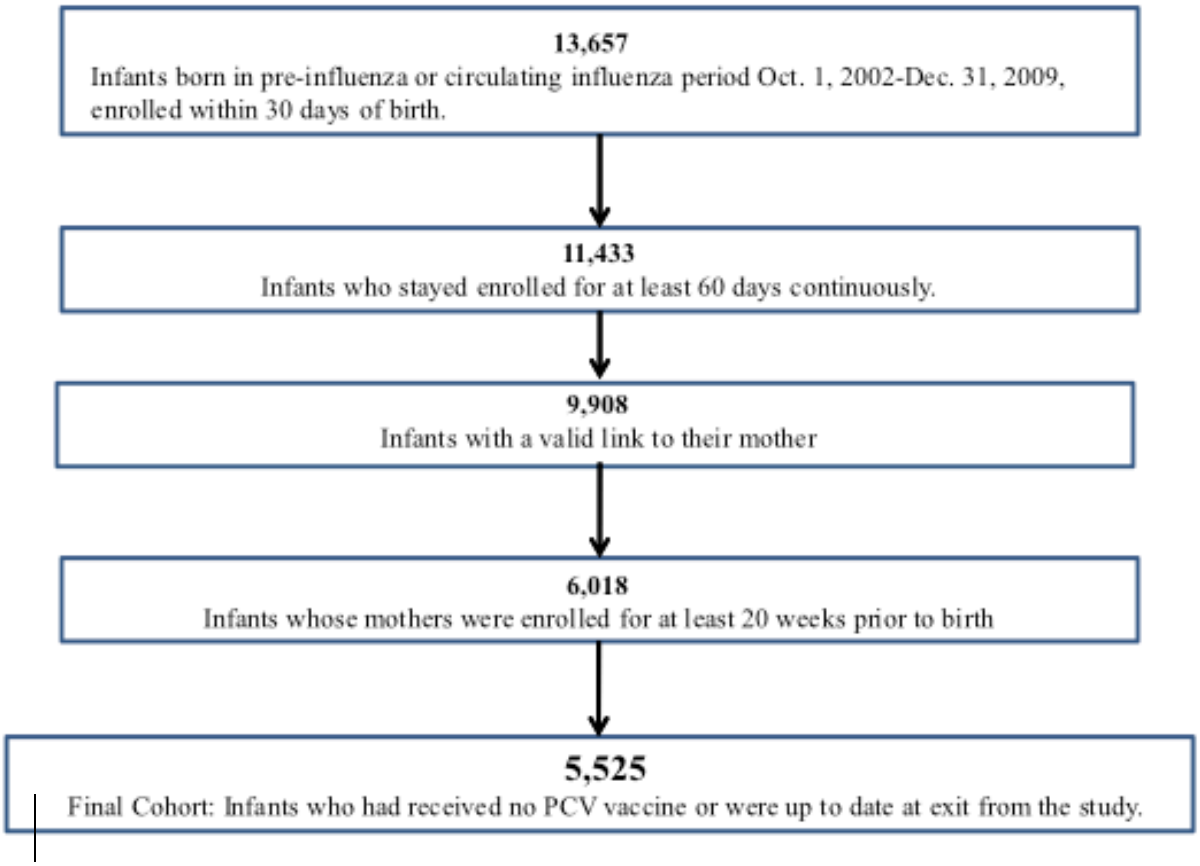

Figure 1: Cohort creation from births during periods of pre-influenza circulation or influenza circulation from October 1, 2002 to December 31, 2009

Table 1: Cohort births during pre-influenza activity periods and periods of at last local influenza activity, shown for each influenza season including H1N1 births. N=5,525

Season	Pre-influenza activity	Pre-influenza births	At least local influenza activity	Influenza circulation births
2002-2003			Oct 1 - Apr 26	744
2003-2004	Oct 1 - Nov 7	86	Nov 8 - Jan 21	232
2004-2005	Oct 1 - Jan 14	363	Jan 15 - Mar 31	290
2005-2006	Oct 1 - Dec 21	279	Dec 22 - Apr 14	510
2006-2007	Oct 1 - Nov 7	119	Nov 8 - Apr 7	668
2007-2008	Oct 1 - Dec 31	358	Jan 1 - Apr 14	472
2008-2009	Oct 1 - Jan 21	424	Jan 22 - Mar 21	252
			Apr 29 - Sep 30*	405
2009-2010			Oct 1 - Dec 31*	323
Overall		1,629 (29%)		3896 (71%)

*Births from April 29, 2009 to December 31, 2009 were considered H1N1 influenza ciruclation activity births and were excluded in the non H1N1 analysis.

Table 2: Maternal nfluenza vaccination coverage, infant PCV vaccination coverage, acute otitis media coverage, and medically attended acute respiratory infection (MAARI) coverage for outcomes after 2 months of age. by influenza season. H1N1 births included. N=5,525

Flu Season	Overall	2002-2003	2003-2004	2004-2005	2005-2006	2006-2007	2007-2008	2008-2009	H1N1 (not during influenza season)	2009-2010
Influenza Coverage n (%)	1788 (32%)	59 (8%)	47 (15%)	208 (32%)	262 (33%)	310 (39%)	329 (40%)	242 (36%)	127 (31%)	204 (63%)
PCV: Up to date n (%)	4508 (82%)	525 (71%)	251 (79%)	610 (93%)	657 (83%)	653 (83%)	687 (83%)	539 (80%)	317 (78%)	269 (83%)
Acute Otitis Media										
Total number of cases	2,771	394	109	381	419	407	419	287	206	149
Average number of cases* n (SD)	1.4 (0.8)	1.4 (0.8)	1.4 (0.8)	1.5 (0.9)	1.4 (0.8)	1.4 (0.9)	1.4 (0.7)	1.4 (0.8)	1.5 (0.8)	1.4 (1)
Infants with no cases n (%)	3559 (64%)	457 (61%)	240 (75%)	396 (61%)	485 (61%)	500 (64%)	526 (63%)	472 (70%)	265 (65%)	218 (67%)
MAARI										
Total number of cases	4,121	615	198	617	618	564	583	438	279	209
Average number of cases* n (SD)	1.6 (1)	1.7 (1.1)	1.6 (0.9)	1.8 (1.1)	1.6 (1)	1.5 (0.9)	1.6 (0.9)	1.5 (0.8)	1.6 (0.8)	1.6 (1.1)
Infants with no cases n (%)	2976 (54%)	386 (52%)	191 (60%)	306 (47%)	412 (52%)	422 (54%)	459 (55%)	382 (57%)	226 (56%)	192 (59%)
Total infant births in season	5,525	744	318	653	789	787	830	676	405	323

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Infants with no cases n (%)	3559 (64%)	457 (61%)	240 (75%)	396 (61%)	485 (61%)	500 (64%)	526 (63%)	472 (70%)	265 (65%)	218 (67%)
MAARI										
Total number of cases	4,121	615	198	617	618	564	583	438	279	209
Average number of cases* n (SD)	1.6 (1)	1.7 (1.1)	1.6 (0.9)	1.8 (1.1)	1.6 (1)	1.5 (0.9)	1.6 (0.9)	1.5 (0.8)	1.6 (0.8)	1.6 (1.1)
Infants with no cases n (%)	2976 (54%)	386 (52%)	191 (60%)	306 (47%)	412 (52%)	422 (54%)	459 (55%)	382 (57%)	226 (56%)	192 (59%)
Total infant births in season	5,525	744	318	653	789	787	830	676	405	323

Table 3: Covariate distribution by vaccination exposure group: maternal influenza vaccination (TIV) and infant pneumococcal vaccine (PCV) for pre-influenza circulation period births and births during the period of influenza circulation from Oct. 1, 2002-2009. N=5,525

		Vaccination group at end of follow up			
	Full Cohort	**PCV-TIV- (REFERENT)**	**PCV-TIV+**	**PCV+TIV-**	**PCV+TIV+**
Mother-Infant Pairs enrolled n (%)	5,525	902 (16%)	115 (2%)	2835 (51%)	1673 (30%)
Person-Time Contributed:					
Median Days (IQR)	365 (320,365)	289.5 (131,365)	365 (133,365)	365 (365,365)	365 (365,365)
Mean Days (SD)*	316.6 (91.3)	250.8 (117.3)	266.4 (117.9)	329 (79)	334.6 (74.1)
Infants with less than 1 year of enrollment n(%)*	1553 (28%)	529 (59%)	57 (50%)	651 (23%)	316 (19%)
Average num. of pediatric visits in first year					
Non-Outcome Sick visits⊗†* n (SD)	6.3 (4.1)	4.7 (3.7)	6.5 (4.4)	6.2 (4)	7.4 (4.1)
Well visits⊗†* n (SD)	3.3 (1.7)	2.5 (1.8)	2.7 (1.9)	3.4 (1.6)	3.6 (1.6)
Infant flu vacc. status (from 6 mo. age)					
Vaccinated* n (%)	1382 (25%)	7 (1%)	5 (4%)	526 (19%)	844 (50%)
Infant's Sex*					
Male n (%)	2894 (52%)	500 (55%)	67 (58%)	1467 (52%)	860 (51%)
Mothers Race (imputed)⊗					
White n (%)	1759 (32%)	304 (34%)	28 (24%)	913 (32%)	514 (31%)
Black* n (%)	1307 (24%)	219 (24%)	30 (26%)	672 (24%)	386 (23%)
Other* n (%)	724 (13%)	99 (11%)	16 (14%)	384 (14%)	225 (13%)
Unknown n (%)	1735 (31%)	280 (31%)	41 (36%)	866 (31%)	548 (33%)
Infant's Race (imputed)⊗					
White n (%)	1692 (31%)	289 (32%)	38 (33%)	837 (30%)	528 (32%)
Black* n (%)	1235 (22%)	200 (22%)	17 (15%)	650 (23%)	368 (22%)
Other* n (%)	617 (11%)	92 (10%)	8 (7%)	333 (12%)	184 (11%)
Unknown n (%)	1981 (36%)	321 (36%)	52 (45%)	1015 (36%)	593 (35%)
Average Mother's age n (SD)	31.1 (5.6)	30.5 (5.7)	31.6 (4.6)	31 (5.8)	31.7 (5)
Multiple Births					
Singleton n (%)	4220 (76%)	693 (77%)	85 (74%)	2166 (76%)	1276 (76%)
Multiple* n (%)	138 (3%)	26 (3%)	4 (3%)	64 (2%)	44 (3%)
Unknown* n (%)	1167 (21%)	183 (20%)	26 (23%)	605 (21%)	353 (21%)
Previous Births to Mother					
First Birth* n (%)	112 (7%)	118 (13%)	7 (6%)	447 (16%)	112 (7%)

⊗All adjusted poisson regression models included: Non-outcome sick visits, well visits, infant's sex, and mother's race based on a priori criteria.

† Non-outcome well-visits and sick visits were truncated at a maximum of 6 well visits and 15 sick visits

∗Significant at α=0.05

Table 4: Adjusted IRRs, ratio of IRRs (R-IRR) and vaccine effectiveness for pre-influenza circulation period births and births during the period of influenza circulation from Oct. 1, 2002-Dec. 31, 2009. Estimates are adjusted for the number of non-outcome infant sick visits in the study period, number of infant well visits in the study period, mother's race, and infant's sex.

Cohort	Vaccination Group	N	Vaccine Effectiveness	AOM R-IRR (95% CI)	IRR for pre-influenza period (95% CI)	IRR for ciruclating influenza period (95% CI)	Vaccine Effectiveness	MAARI R-IRR (95% CI)	IRR for pre-influenza period (95% CI)	IRR for circulating influenza period (95% CI)
All pre-influenza and influenza season births, including H1N1 **N=5,525**	PCV-TIV-	902	REFERENT	REFERENT	REFERENT	REFERENT	REFERENT	REFERENT	REFERENT	REFERENT
	PCV-TIV+	115	10.9% (-176.8 , 71.3)	0.89 (0.29 , 2.77)	1.15 (0.5 , 2.66)	1.02 (0.74 , 1.42)	35.5% (-40.5 , 70.4)	0.64 (0.30 , 1.4)	1.23 (0.69 , 2.18)	0.79 (0.59 , 1.06)
	PCV+TIV-	2,835	13.9% (-24.7 , 40.6)	0.86 (0.59 , 1.25)	1.22 (0.92 , 1.6)	1.05 (0.9 , 1.21)	4.4% (-20 , 23.8)	0.96 (0.59 , 1.25)	1 (0.82 , 1.22)	0.96 (0.85 , 1.08)
	PCV+TIV+	1,673	35.7% (-3.3 , 60)	0.64 (0.40 , 1.03)	1.58 (1.19 , 2.09)	1.02 (0.87 , 1.19)	17.8% (-6.7 , 36.7)	0.82 (0.41 , 1.09)	1.14 (0.93 , 1.39)	0.93 (0.82 , 1.06)
Pre-influenza and influenza season births, *excluding* H1N1 births.* **N=4,797**	PCV-TIV-	783	REFERENT	REFERENT	REFERENT	REFERENT	REFERENT	REFERENT	REFERENT	REFERENT
	PCV-TIV+	92	7.1% (-192.6 , 70.5)	0.93 (0.29 , 2.9)	1.15 (0.5 , 2.66)	1.06 (0.75 , 1.52)	7.1% (-192.6 , 70.5)	0.59 (0.27 , 1.29)	1.23 (0.69 , 2.18)	0.73 (0.52 , 1.01)
	PCV+TIV-	2,557	14.1% (-25.3 , 41.1)	0.86 (0.59 , 1.25)	1.22 (0.92 , 1.6)	1.04 (0.89 , 1.23)	14.1% (-25.3 , 41.1)	0.94 (0.74 , 1.18)	1 (0.82 , 1.22)	0.94 (0.83 , 1.07)
	PCV+TIV+	1,365	33% (-8.6 , 58.7)	0.67 (0.41 , 1.09)	1.58 (1.19 , 2.09)	1.06 (0.89 , 1.26)	33% (-8.6 , 58.7)	0.81 (0.62 , 1.06)	1.14 (0.93 , 1.39)	0.92 (0.81 , 1.06)

*Births excluded from the H1N1 analysis were those that occurred from April 27, through December 31, 2009.

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SUPPLEMENTARY MATERIALS

Supplement Table 1: Adjusted IRRs, ratio of IRRs (R-IRR) and vaccine effectiveness for the average of pre-influenza circulation period births in infants born from Oct 1, 2002-December 31, 2009 and births during the period of H1N1 influenza circulation from April 29, 2009-Dec. 31, 2009 . Estimates are adjusted for the number of non-outcome infant sick visits in the study period, number of infant well visits in the study period, mother's race, and infant's sex. N=728.

	N	Vaccine Effectiveness	AOM R-IRR (95% CI)	IRR for pre-influenza period (95% CI)	IRR for circulating influenza period (95% CI)	Vaccine Effectiveness	MAARI R-IRR (95% CI)	IRR for pre-influenza period (95% CI)	IRR for ciruclating influenza period (95% CI)
PCV-TIV-	308	REFERENT	REFERENT	REFERENT	REFERENT	REFERENT	REFERENT	REFERENT	REFERENT
PCV-TIV+	278	39.8% (-114.8 , 83.1)	0.6 (0.17 , 2.15)	1.15 (0.5 , 2.66)	0.69 (0.29 , 1.63)	23.1% (-107 , 71.5)	0.77 (0.29 , 2.07)	1.15 (0.5 , 2.66)	0.94 (0.49 , 1.81)
PCV+TIV-	23	23.5% (-23.3 , 52.6)	0.76 (0.47 , 1.23)	1.22 (0.92 , 1.6)	0.93 (0.65 , 1.33)	5.9% (-34 , 33.9)	0.94 (0.66 , 1.34)	1.22 (0.92 , 1.6)	0.94 (0.69 , 1.28)
PCV+TIV+	119	45.6% (6.1 , 68.4)	0.54 (0.32 , 0.94)	1.58 (1.19 , 2.09)	0.86 (0.6 , 1.23)	11.8% (-29.7 , 40)	0.88 (0.6 , 1.3)	1.58 (1.19 , 2.09)	1 (0.74 , 1.36)

PUBLIC HEALTH IMPLICATIONS

We have shown a combined interaction of maternal influenza vaccine and infant pneumococcal conjugate vaccine in protecting infants from pneumococcal outcomes, specifically acute otitis media and medically attended acute respiratory infection. Since its introduction in the United States in 2000, PCV has coverage in the United States has increased dramatically and is now estimated to be 90%. In order to provide the most protection for infants in the United States, maternal influenza vaccination must also increase to reach PCV coverage levels. This study shows that protection of infants from respiratory disease begins while they are still in the womb, and advocates maternal influenza vaccination.

KAISER PERMANENTE OF GEORGIA INSTITUTIONAL REVIEW BOARD APPROVAL

KAISER PERMANENTE®

NOTIFICATION OF APPROVAL

November 2, 2011

To: Saad Omer

CC: Dzifa Adjaye-Gbewonyo

Re: Study ID: GA-11SOmer-01
Modification ID: MR1_GA-11SOmer-01
Study Title: Vaccine Safety Datalink

The study modification regarding a new protocol for the Maternal TIV Infant PCV substudy and a revised protocol for the HPV and Behaviors Study substudy was reviewed and approved by the Kaiser Permanente Georgia Institutional Review Board (KPGA IRB) expedited review procedures on October 27, 2011.

The IRB waived the requirement to obtain informed consent and the requirement for written Privacy Rule authorization for the Maternal TIV Infant PCV substudy.

Please use this notification of approval should the funding agency require documentation of IRB approval. Our Federalwide Assurance number is FWA 00002344 – IRB 00000406.

Kaiser Permanente Georgia IRB
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