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Maternal Influenza Immunization and Prevention of Severe Clinical Pneumonia in Young Infants: Analysis of Randomized Controlled Trials Conducted in Nepal, Mali, and South Africa

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Abstract (Word Count: 250/250)

Background: To evaluate the effect of antenatal influenza vaccination on all-cause severe infant pneumonia, we performed pooled analysis of three randomized-controlled trials conducted in Nepal, Mali, and South Africa.

Methods: The trials were coordinated from the planning phase. The follow-up period was 0–6 months post-partum in Nepal and Mali, and 0-24 weeks in South Africa. Pregnant women with gestational age 17-34 weeks in Nepal, ≥ 28 weeks in Mali, and 20-36 weeks in South Africa were enrolled. Trivalent Inactivated Influenza Vaccine (IIV). was compared with either saline placebo (Nepal and South Africa) or quadrivalent meningococcal conjugate vaccine (MCV) (Mali). In South Africa, cases were hospitalized, and were therefore considered to have severe pneumonia. In Nepal and Mali, severe infant pneumonia diagnosis was based on the WHO Integrated Management of Childhood Illness (IMCI) definition.

Results: A total of 10,002 mothers and 9,801 live-born eligible infants were included in the present analysis. Incidence rate of severe pneumonia was 31% lower in the IIV group compared to the control group (incidence rate ratio [IRR]: 0.69, 95% CI: 0.50 - 0.94, $P = 0.02$). During periods with high influenza circulation there was lower incidence of severe pneumonia among the IIV group (IRR: 0.20, 95% CI: 0.06 - 0.74, $P = 0.02$), however, there was no difference in pneumonia incidence between study groups during periods of low and no influenza circulation.

Conclusions: Maternal influenza immunization may reduce severe pneumonia episodes among infants –particularly those too young to be completely vaccinated against *S. pneumoniae* and influenza.

Trial Registration: The three trials were registered with ClinicalTrials.gov (trial numbers NCT01430689, NCT01034254, NCT02465190).

Introduction

Pneumonia is an important cause of morbidity and mortality in young children. *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) polysaccharide-protein conjugate vaccines have reduced the pneumonia burden in high and low-middle income countries.¹ However, there are limits to the potential success of these conjugate vaccines, including that a significant proportion of pneumonia etiologies are not covered by these vaccines.² Moreover, not all pneumococcal serotypes responsible for infant pneumonia are included in the various licensed formulations of the pneumococcal conjugate vaccine (PCV).

Influenza immunization during pregnancy could serve as an additional tool to reduce pneumonia-associated morbidity and mortality, particularly in young infants. There are biological, clinical, and epidemiological reasons to consider maternal influenza immunization for protection against infant pneumonia. For example, there is evidence that influenza infection predisposes individuals to pneumococcal infection.³ In fact, a considerable proportion of mortality during the 1918 influenza pandemic may have been due to secondary bacterial infection, including *Haemophilus influenzae*, *S. pneumoniae*, *Streptococcus pyogenes*, and/or *Staphylococcus aureus*.^{3,4} It is plausible that influenza immunization during pregnancy can attenuate the risk of pneumonia in young infants by reducing the incidence of influenza virus infection -a risk factor for secondary bacterial pneumonia.

While the efficacy of influenza vaccine administered in pregnancy to protect infants against laboratory-confirmed influenza has been demonstrated in four randomized-controlled trials, these trials were not specifically designed to have the power to detect an impact on infant pneumonia.⁵⁻⁸ Of these trial sites, Nepal had an incidence between 239 and 255 pneumonia cases per 1,000 children from 2009 to 2011 in children under 5 years of age, and Mali had an incidence

of 0.32 pneumonia episodes per child-year (95% CI: 0.16, 0.74) in children under 4 years of age. Similarly, from 2009 to 2012 South Africa had a lower respiratory tract infection (LRTI) hospitalization incidence of 2530 to 3173 per 100,000 children under 5 years.⁹⁻¹¹ In this manuscript, we present a pooled analysis of three randomized-controlled trials with an adequate combined sample size to evaluate the effect of influenza vaccine administered in pregnancy on infant pneumonia.

Methods

Methods, procedures, and initial results for each of three clinical trials have been previously described in detail (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/C951>).^{6-8,12} Briefly, the three randomized-controlled Maternal Influenza Immunization trials were designed as separate studies. The Nepal trial was conducted as two annual cohorts that were combined to determine vaccine efficacy.⁸ However, from the planning phase onward, the investigators from all three trials coordinated the study protocols and procedures to ensure future comparisons of the results. Moreover, pooled analysis of selected study outcomes was planned prior to the completion of the trials. An overview of the planned pooled analysis has been previously published.¹² The pooled analysis was planned in order to better understand the benefits of maternal IIV, particularly for pneumonia in infants for which the individual trials were not powered.¹² This pooled analysis will also have many advantages over a meta-analysis, as pooled analysis allows for better standardization of analytical variables, more robust confounder control, and greater ability to evaluate heterogeneity and effect modification. The pooled analysis had a 90% power to detect a 30% change in severe infant pneumonia, based on a combined cohort size of 10,000 and baseline incidence of around 0.1 cases per infant-year.¹²

The trials screened and enrolled pregnant women from nine Village Development Committees in the rural Terai region of southern Nepal and from pregnant women accessing prenatal care in urban Bamako, Mali and Soweto, South Africa. In Nepal, pregnant women at 17 - 34 weeks in gestation were included, in Mali, pregnant women in their third trimester (gestational age \geq 28 weeks) were included, and in South Africa, pregnant women with gestational ages between 20 - 36 weeks were included. Enrollment began in late April 2011 in Nepal, early September 2011 in Mali, and early March 2011 in South Africa. Infants born to the enrolled mothers were followed up to 6 months of age in Nepal and Mali, and 24 weeks in South Africa, with follow up ending in early May 2014 in Nepal, late January 2014 in Mali, and late May 2013 in South Africa. For the pneumonia outcome, infants at all sites were assessed for pneumonia through weekly home visits, as well as by hospital based surveillance in South Africa.

Women were randomized to receive Trivalent Inactivated Influenza Vaccine (IIV) in the intervention group of all three trials. Women in the control groups in Nepal and South Africa received saline placebo; whereas, women in the control group in Mali received quadrivalent meningococcal conjugate vaccine (MCV). The two annual cohorts of mothers enrolled in Nepal received IIV throughout the year because of the subtropical setting with influenza virus circulation for many months each year.¹² Women were vaccinated year-around as well in Mali.¹² Vaccinations were given to correspond with peak influenza periods in South Africa.¹² In Nepal, influenza was detected from July 2011 to April 2012, July 2012 to November 2012, February and March 2013, and from May 2013 to November 2013.⁸ In Mali, months with higher-than-average influenza rates were from February to April, and from September to October in 2012.⁷ In

South Africa, the 2011 influenza season was from May to November, and the 2012 season continued from May to October.^{6,13}

There were differences between the three sites in terms of collecting information on non-severe pneumonia, therefore we restricted the analyses to severe pneumonia. In Nepal and Mali, severe pneumonia was based on the 2004 Integrated Management of Childhood Illness (IMCI) definition: cough or difficulty breathing plus any danger sign (unable to drink/nurse, vomits everything, convulsions, lethargy, or unconsciousness) or lower chest indrawing or stridor (data on stridor was not available across all sites). To be considered severe pneumonia in Nepal, the number of days between the last day a child exhibited a morbidity sign during an episode and the date the case report form had to be less than or equal to 14 days. In South Africa, all cases of pneumonia, (International Classification of Disease, Tenth Revision code of pneumonia, bronchiolitis, or an unspecified acute lower respiratory tract infection) were hospitalized, and were therefore considered to have severe pneumonia.¹³ Data on non-severe pneumonia were not collected. The 2004 IMCI definition was used because it was the current definition at the time of these studies. To determine the rate of hospitalization in Nepal and Mali, any hospitalization following an episode of severe pneumonia was considered.

Laboratory-confirmed influenza was detected through PCR assays.¹² Active influenza circulation was defined as any week with at least one positive influenza test in mother or infant in the study. In addition to stratifying by weeks with any and no influenza circulation, periods with any circulation were further stratified into high circulation weeks ($\geq 0.25\%$ of subjects tested positive for influenza in a week of the subjects at risk), and low circulation weeks (0 to 0.25% of subjects tested positive for influenza in a week of the subjects at risk). Given that the trials included active, aggressive surveillance, the conventional cutoffs for passive surveillance

were not applicable. Teams from all sites choose the 0.25% to ensure that there are sufficient high and low weeks across sites. In Nepal, individuals were considered not at risk for each day of an illness episode following the incident day through seven asymptomatic days following the last day of symptoms. For consistency in assessing intensity of influenza circulation, for each site we determined the number at risk for acquiring influenza per week as the number of mothers and infants in the study for that week.

Poisson regression models were used to find incidence rate ratios (IRR), and log-binomial regressions were used to find risk ratios (RR). Robust confidence intervals were used, and pooled estimates were adjusted for the main effect of each site, as well as interaction by site. Vaccine efficacy (VE) was calculated as: $[(1-IRR) \times 100]$. The number needed to vaccinate (NNV), was calculated as: $1/[\text{incidence in the unvaccinated} \times (\text{vaccine efficacy})]$. The proportion hospitalized was calculated as: $[(\text{infants hospitalized}/\text{total pneumonia cases}) \times 100]$, and included any hospitalization that occurred in an infant who had an episode of severe pneumonia. Kaplan-Meier time-to-event analyses was used to show time from birth to the first episode of severe pneumonia across the intervention groups, and compared using log-rank tests. Infants were administratively censored at 180 days of age for Nepal and Mali, and at 175 days of age for South Africa as per protocol. Statistical analyses were performed using Stata version 14.2 (Stata Corp., College Station, Texas, USA), and alpha level of 0.05 was used. The study protocols were reviewed and approved by institutional review boards from the partner entities involved in this analysis.^{6-8,12} The three trials were registered with ClinicalTrials.gov (trial numbers NCT01430689, NCT01034254, NCT02465190).

Results

A total of 10,002 mothers (5,017 received IIV vaccine and 4,985 received control) were enrolled, and 9,800 total live eligible infants were born (4,910 live-births, including 76 pairs of twins, to mothers who received IIV, and 4,890 live-births, including 76 pairs of twins, to mothers who received control) (Figure 1). Infants who were stillborn were excluded from the analysis (71 stillborn infants in the IIV group, and 70 in the control), as were miscarriages (8 miscarriages in the IIV group, and 8 miscarriages in the control), abortions (0 abortions in the IIV group, and 1 abortion in the control), and infants of women who withdrew or were lost to follow up prior to the start of the study (104 in the IIV group, and 92 in the control). Distribution of maternal characteristics has been described previously and was similar between the two intervention groups in terms of maternal age, gestational age, and maternal nutritional status at enrollment.^{6-8,12}

In Nepal, there was incidence rate of 123.7 severe pneumonia cases per 1,000 infant-years among the control group, while the control group in Mali had an incidence rate of 61.4 cases per 1,000 infant-years, and the control group in South Africa had an incidence rate of 70.9 cases per 1,000 infant-years (Table, Supplemental Digital Content 2, <http://links.lww.com/INF/C952>). The incidence rate across the control groups three sites was 87.7 cases per 1,000 infant-years. Overall, incidence rate of severe pneumonia, with adjustment for the main effects of site and interaction by site, was 31% lower in the IIV group compared to the control group (pooled incidence rate ratio: 0.69, 95% CI: 0.50 - 0.94, $p = 0.02$; pooled vaccine efficacy: 31.3%, 95% CI: 6.4% - 49.6%) (Table 1). There was no difference in time to first episode of severe infant pneumonia in the intervention group compared to the control group (Figure 2). Calculations of the number needed to vaccinate indicated that to prevent one episode

of severe pneumonia, 109 pregnant women need to be vaccinated.

When restricted to weeks with any influenza circulation, the incidence rate of severe pneumonia, with adjustment for the main effects of site and interaction by site, was 41% lower in the IIV group compared to the control group (pooled incidence rate ratio: 0.59, 95% CI: 0.39 - 0.88, $p = 0.01$; pooled vaccine efficacy 40.9%, 95% CI: 11.6% - 60.5%) (Table 1). During weeks without influenza circulation, there was no association between receipt of maternal IIV and infant severe pneumonia (pooled incidence rate ratio: 0.87, 95% CI: 0.53 - 1.43, $p = 0.58$; pooled vaccine efficacy 13.0%, 95% CI: -43.3% - 47.2%) (Table 1).

Further stratifying periods of any influenza circulation into high and low circulation, during weeks with high influenza circulation, the incidence rate of severe pneumonia was 80% lower in the IIV group compared to the control group (pooled incidence rate ratio: 0.20, 95% CI: 0.06 - 0.74, $p = 0.02$; pooled vaccine efficacy 79.6%, 95% CI: 25.8% - 94.4%) (Table 1). In contrast, there was no difference in severe pneumonia incidence in the IIV group compared to the control group in periods of low influenza circulation (IRR: 0.69, 95% CI: 0.45 - 1.06, $P = 0.09$) (Table 1).

Of the cases in the intervention group, 34.6% were eventually hospitalized, and of the cases in the control group, 35.5% were eventually hospitalized. 100% of the cases in South Africa were hospitalized.

Discussion

Overall, we found influenza immunization during pregnancy to be protective against severe clinical pneumonia among young infants. The overall calculations of NNV indicated that to prevent an episode of severe pneumonia among infants younger than 6 months, 109 pregnant women need to be vaccinated. In comparison, the estimated NNV for pneumococcal conjugate

vaccine in a randomized controlled trial in Gambia was approximately 68 for preventing radiologically confirmed pneumonia and 364 for radiologically confirmed severe pneumonia over a mean follow up of 87 weeks after vaccination at 6, 10, and 14 weeks of age.¹⁴ Hib vaccination was implemented in Nepal, and Hib and PCV vaccination were implemented in Mali and South Africa at the time of the study.¹⁵ From 2011 to 2014, rates of Hib vaccination in the general population ranged from 90 to 92% in Nepal, 76 to 90% in Mali, and 83 to 95% in South Africa.¹⁵ During this time frame, rates of PCV vaccination ranged from 56 to 87% in Mali, and 80 to 90% in South Africa.¹⁵

Our overall findings are supported by earlier evidence. For example in a mouse model, influenza infection a week prior to pneumococcal infection showed higher mortality rates compared to pneumococcal infection alone and to simultaneous infection with influenza and *S. pneumoniae*.¹⁶ This mouse model has also shown that pulmonary production of interferon γ as a result of T cell responses to influenza infection inhibits pneumococcal clearance by alveolar macrophages.¹⁷ This virus-bacteria synergy has been observed in human clinical and epidemiological studies as well.^{18,19}

The role of influenza immunization during pregnancy for preventing infant respiratory illnesses associated with secondary bacterial infections has been explored for syndromes other than pneumonia. In a randomized controlled trial with a two by two factorial design conducted in Bangladesh, the combined efficacy of maternal influenza vaccine and infant pneumococcal vaccine was 45.5% (95% CI: 8.7% – 67.5%) against medically attended acute respiratory illness (MAARI) during the full study period, and 66.4% (95% CI: 14.3% – 86.9%) during the influenza circulation period.²⁰ Whereas, there was no significant protection against MAARI in the maternal influenza vaccine only group and the infant pneumococcal vaccine only group.²⁰ Similarly, in an

observational study in the United States where influenza circulation was taken into account, vaccine effectiveness against MAARI was 39.6% (95% CI: 31.6% - 46.7%) for the maternal influenza vaccine plus infant pneumococcal conjugate vaccine group compared to 29.8% (95% CI: 11.4% - 44.3%) effectiveness in the infant pneumococcal vaccine only group.²¹

Caution should be used in interpreting our results, as large studies of pneumonia do not ascribe 31% of cases of severe pneumonia in young children to influenza. There is a gap in data from clinical trials in developing countries in establishing the role of influenza in directly or indirectly affect pneumonia. The vaccine effect may also differ across geography, due to varying disease burden and heterogeneity in vaccine efficacy. Another limitation to this study is some inconsistencies in data available across study sites, including the reason for infant hospitalization. There also were different surveillance methods used to detect severe pneumonia between Nepal and Mali versus South Africa. However, a pooled analysis allowed for better standardization of analytical variables over a traditional meta-analysis, as well as provided the power to detect a difference in severe pneumonia.

Conclusion: Given the high morbidity, mortality, and economic burden associated with infant pneumonia (and influenza illness), maternal influenza immunization can serve as a potential tool to reduce severe health outcomes among infants, particularly those too young to be completely vaccinated against *S. pneumoniae* and influenza. However, broad introduction of maternal influenza immunization in low and middle income countries will require data on the effect of maternal influenza immunization in a variety of settings, as well as more effective influenza vaccines.

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Table 1. Pooled¹ incidence per 1000 infant-years, incidence rate ratio² and vaccine efficacy severe infant pneumonia³ over 180-day⁴ follow-up by levels of influenza circulation

	<u>Intervention</u>			<u>Control</u>			Incidence Rate Ratio ⁶ (95% Confidence Interval)	Vaccine Efficacy % (95% Confidence Interval)	P-Value
	Cases	No. Infant- Years	Incidence ⁵	Cases	No. Infant- Years	Incidence ⁵			
Overall	162	2292.9	70.7	201	2291.4	87.7	0.69 (0.50, 0.94)	31.3 (6.4, 49.6)	0.02
Any Influenza Circulation	75	2107.5	35.6	120	2128.0	56.4	0.59 (0.39, 0.88)	40.9 (11.6, 60.5)	0.01
No Influenza Circulation	87	2245.6	38.7	81	2237.6	36.2	0.87 (0.53, 1.43)	13.0 (-43.3, 47.2)	0.58
High Influenza Circulation	13	1515.8	8.6	31	1547.9	20.0	0.20 (0.06, 0.74)	79.6 (25.8, 94.4)	0.02
Low Influenza Circulation	62	1997.3	31.0	89	2000.0	44.5	0.69 (0.45, 1.06)	30.9 (-6.1, 55.0)	0.09

¹ Adjusted for site and interaction by site

² IRRs calculated with Poisson model

³ Severe pneumonia is defined according to 2004 IMCI

⁴ 175-day follow-up in South Africa

⁵ Per 1000 infant years

⁶ Reference: control group

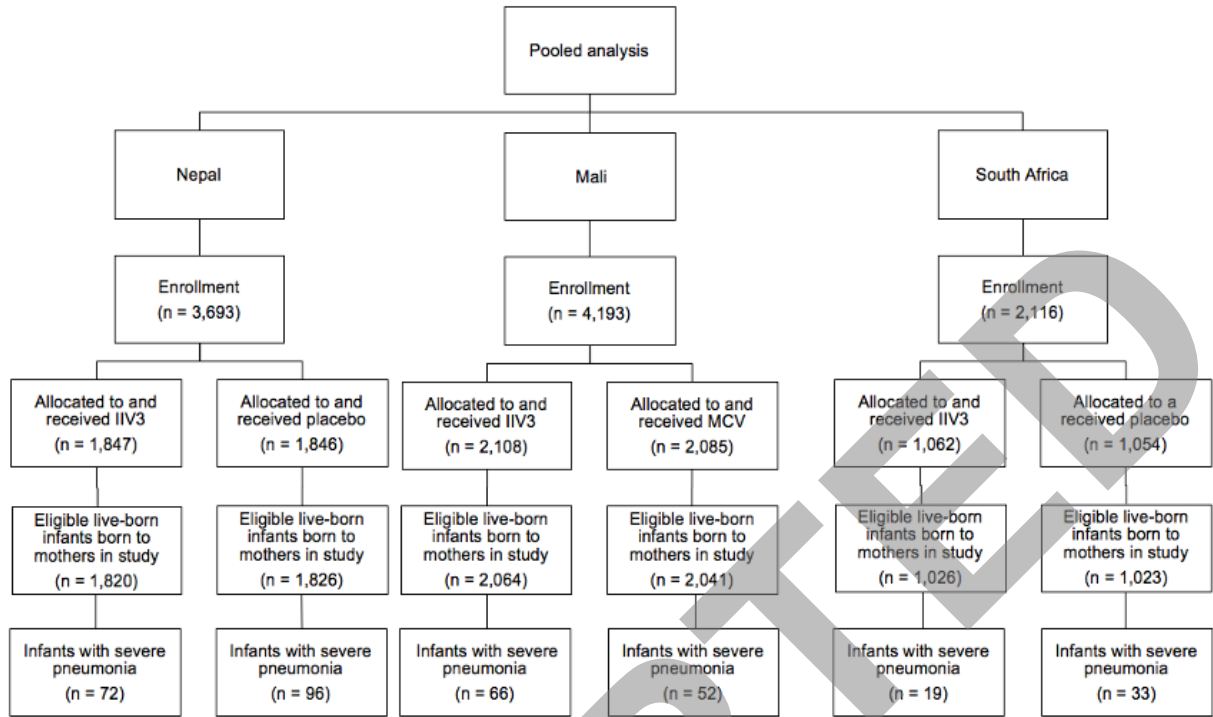


Figure 1. Trial

profile

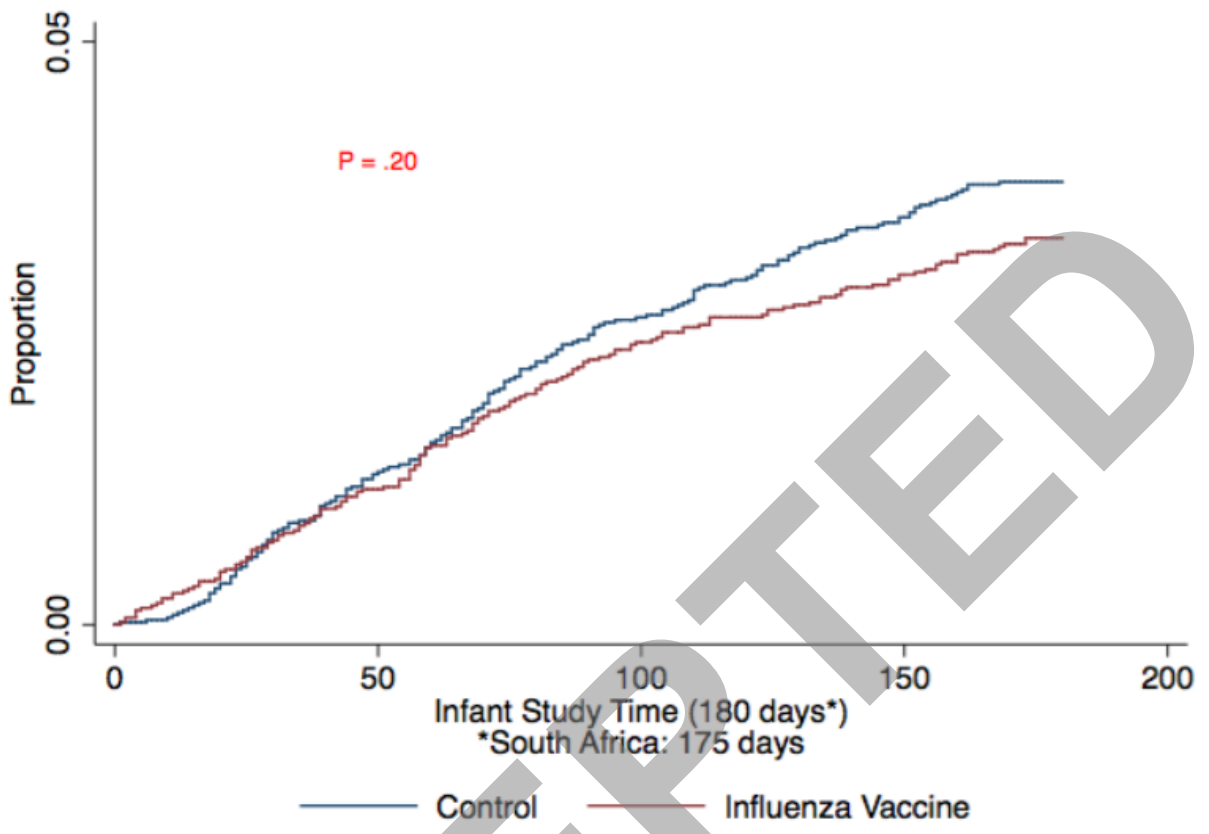


Figure 2. Kaplan-Meier time-to-severe infant pneumonia