# Maternal Influenza Immunization and Prevention of Severe Clinical Pneumonia in Young Infants

## Analysis of Randomized Controlled Trials Conducted in Nepal, Mali and South Africa

*Saad B. Omer, MBBS, MPH, PhD,*\*†‡§ *Dayna R. Clark, MPH,*† *Anushka R. Aqil, MPH,*\* *Milagritos D. Tapia, MD,*¶‖ *Marta C. Nunes, PhD,*\*\*†† *Naoko Kozuki, PhD,*‡‡ *Mark C. Steinhoff, MD,*‡‡§§ *Shabir A. Madhi, PhD,*\*\*††¶¶ *and Niteen Wairagkar, MD*‖‖*; for BMGF Supported Maternal Influenza Immunization Trials Investigators Group*

**Background:** To evaluate the effect of antenatal influenza vaccination on all-cause severe infant pneumonia, we performed pooled analysis of 3 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 postpartum 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 (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 definition.

**Results:** A total of 10,002 mothers and 9801 live-born eligible infants were included in the present analysis. There was a 31% lower incidence rate of severe pneumonia in the IIV group compared with the control group in Nepal [incidence rate ratio (IRR): 0.69; 95% CI: 0.50–0.94; Table 1]. In South Africa, there was a 43% lower incidence rate of severe pneumonia in the IIV group versus the control group (IRR: 0.57; 95% CI: 0.33–1.0). There was no difference in incidence rates between the IIV group and the control group in Mali. Overall, incidence rate of severe pneumonia was 20% lower in the IIV group compared with the control group (IRR: 0.80; 95% CI: 0.66–0.99; $P = 0.04$). Protection was highest in the high influenza circulation period (IRR: 0.44; 95% CI: 0.23–0.84).

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

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-income and low- to 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 biologic, clinical and epidemiologic 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 because of secondary bacterial infection, including *H. 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.

Although the efficacy of influenza vaccine administered in pregnancy to protect infants against laboratory-confirmed influenza has been demonstrated in 4 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 1000 children from 2009 to 2011 in children younger than 5 years, and Mali had an incidence of 0.32 pneumonia episodes per child-year [95% confidence interval (CI): 0.16–0.74] in children younger than 4 years. Similarly, from 2009 to 2012 South Africa had a lower respiratory tract infection hospitalization incidence of 2530 to 3173 per 100,000 children younger than 5 years.[9–11] In this article, we present a pooled analysis of 3 randomized controlled trials with an adequate combined sample size to evaluate the effect of influenza vaccine administered in pregnancy on infant pneumonia.

## MATERIALS AND METHODS

Methods, procedures and initial results for each of 3 clinical trials have been previously described in detail (Table, Supplemental

Digital Content 1, http://links.lww.com/INF/C951).[6–8,12] Briefly, the 3 randomized controlled maternal influenza immunization trials were designed as separate studies. The Nepal trial was conducted as 2 annual cohorts that were combined to determine vaccine efficacy (VE).[8] However, from the planning phase onward, the investigators from all 3 trials coordinated the study protocols and procedures to ensure future comparisons of the results. Moreover, pooled analysis of selected study outcomes was planned before the completion of the trials. An overview of the planned pooled analysis has been previously published.[12] The pooled analysis was planned to better understand the benefits of maternal trivalent inactivated influenza vaccine (IIV), particularly for pneumonia in infants for whom 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 9 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 of gestation were included, in Mali, pregnant women in their third trimester (gestational age ≥28 weeks) were included and in South Africa, pregnant women with gestational ages between 20 and 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 IIV in the intervention group of all 3 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. The 2 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 to March 2013 and May 2013 to November 2013.[8] In Mali, months with higher-than-average influenza rates were from February to April and 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 3 sites in terms of collecting information on nonsevere 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 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 ≤14 days. In South Africa, all cases of pneumonia (International Classification of Diseases, 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 nonsevere pneumonia were not collected. The 2004 Integrated Management of Childhood Illness 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 after an episode of severe pneumonia was considered.

Laboratory-confirmed influenza was detected through polymerase chain reactions.[12] Active influenza circulation was defined as any week with at least 1 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 (≥0.25% of subjects tested positive for influenza in a week of the subjects at risk) and low-circulation weeks (0%–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 after the incident day through 7 asymptomatic days after 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). Pooled estimates were based on random intercept models. VE was calculated as $[(1 - IRR) \times 100]$. The number needed to vaccinate (NNV), was calculated as $1/[\text{incidence in the unvaccinated} \times (VE)]$. The proportion hospitalized was calculated as $[(\text{infants hospitalized/total pneumonia cases}) \times 100]$ and included any hospitalization that occurred in an infant who had an episode of severe pneumonia. Kaplan-Meier time-to-event analyses were 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, TX), and α 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]

## RESULTS

A total of 10,002 mothers (5017 received IIV and 4985 received control) were enrolled, and 9800 total live eligible infants were born (4910 live-births, including 76 pairs of twins, to mothers who received IIV and 4890 live-births, including 76 pairs of twins, to mothers who received control; Fig. 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 before 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 2 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 1000 infant-years among the control group, while the control group in Mali had an incidence rate of 61.4 cases per 1000 infant-years, and the control group in South Africa had an incidence rate of 70.9 cases per 1000 infant-years (Table, Supplemental Digital Content 2, http://links.lww.com/INF/C952). The incidence rate across the control groups of the 3 sites was 87.7
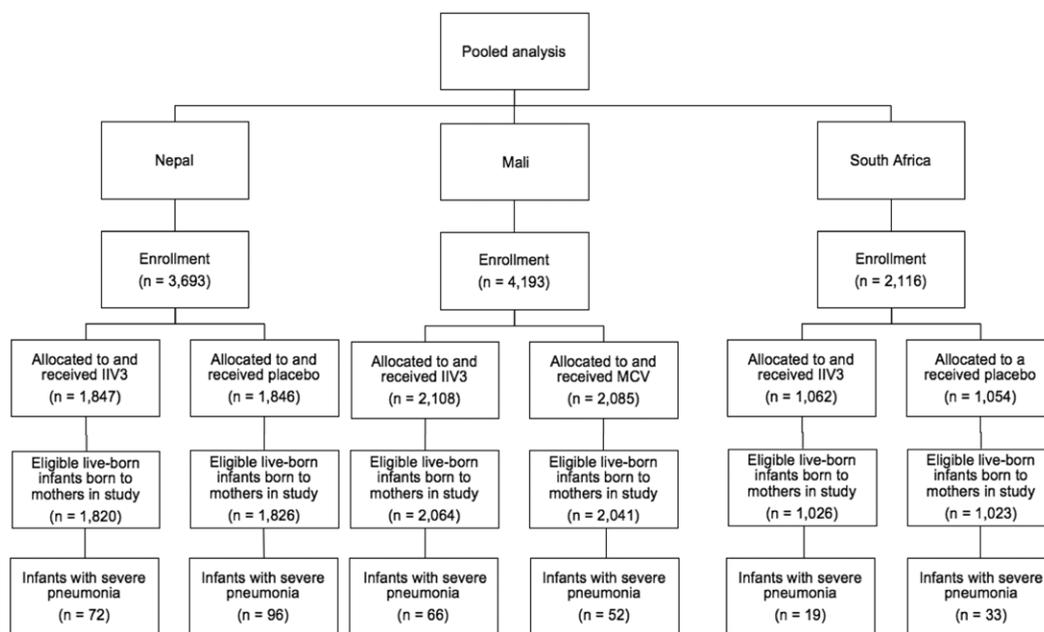
**FIGURE 1.** Trial profile.

**TABLE 1.** Pooled Incidence per 1000 Infant-Years, IRR* and VE Severe Infant Pneumonia† Over 180-Day‡ Follow-up by Levels of Influenza Circulation and by Site

| | Intervention | | | Control | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cases | No. Infant-Years | Incidence§ | Cases | No. Infant-Years | Incidence | IRR¶ (95% CI) | VE % (95% CI) | *P* |
| Overall | 162 | 2292.9 | 70.6 | 201 | 2291.4 | 87.7 | 0.80 (0.66–0.99) | 20 (1–34) | 0.04 |
| By influenza circulation | | | | | | | | | |
|   Any influenza circulation | 75 | 2107.5 | 35.6 | 120 | 2128.0 | 56.4 | 0.63 (0.47–0.84) | 37 (16–53) | 0.002 |
|   No influenza circulation | 87 | 2245.6 | 38.7 | 81 | 2237.6 | 36.2 | 1.07 (0.79–1.45) | −7 (−45 to 21) | 0.66 |
|   High influenza circulation | 13 | 1515.8 | 8.6 | 31 | 1547.9 | 20.0 | 0.44 (0.23–0.84) | 56 (16–77) | 0.01 |
|   Low influenza circulation | 62 | 1997.3 | 31.0 | 89 | 2000.0 | 44.5 | 0.70 (0.50–0.96) | 30 (4–50) | 0.03 |
| By site | | | | | | | | | |
|   Nepal | 76 | 895.0 | 84.9 | 111 | 897.4 | 123.7 | 0.69 (0.50–0.94) | 31 (6–50) | 0.02 |
|   Mali | 67 | 929.9 | 72.0 | 57 | 928.3 | 61.4 | 1.17 (0.81–1.69) | −17 (−69 to 19) | 0.39 |
|   South Africa | 19 | 468.0 | 40.6 | 33 | 465.7 | 70.9 | 0.57 (0.33–1.00) | 43 (0–67) | 0.05 |

*IRRs calculated with Poisson and random intercept model, accounting for site.
†Severe pneumonia is defined according to 2004 WHO Integrated Management of Childhood Illness.
‡175-day follow-up in South Africa.
§Per 1000 infant-years.
¶Reference: control group.

cases per 1000 infant-years. There was a 31% lower incidence rate of severe pneumonia in the IIV group compared with the control group in Nepal (IRR: 0.69; 95% CI: 0.50–0.94; Table 1). In South Africa, there was a 43% lower incidence rate of severe pneumonia in the IIV group versus the control group (IRR: 0.57; 95% CI: 0.33–1.00; Table 1). There was no difference in incidence rates between the IIV group and the control group in Mali. Overall, incidence rate of severe pneumonia was 20% lower in the IIV group compared with the control group (IRR: 0.80; 95% CI: 0.66–0.99; *P* = 0.04; Table 1). There was no difference in time to first episode of severe infant pneumonia in the intervention group compared with the control group (Fig. 2). Calculations of the NNV indicated that to prevent one episode of severe pneumonia, 200 pregnant women need to be vaccinated.

When restricted to weeks with any influenza circulation, the incidence rate of severe pneumonia was 37% lower in the IIV group compared with the control group (pooled IRR: 0.63; 95% CI: 0.47–0.84; Table 1). During weeks without influenza circulation, there was no association between receipt of maternal IIV and infant severe pneumonia (pooled IRR: 1.07; 95% CI: 0.79–1.45; 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 56% lower in the IIV group compared with the control group (pooled IRR: 0.44; 95% CI: 0.23–0.84; Table 1). In periods of low influenza circulation, the incidence rate of severe pneumonia was 30% lower in the IIV group compared with the control group (IRR: 0.70; 95% CI: 0.50–0.96; 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. Hundred percent of the cases in South Africa were hospitalized.
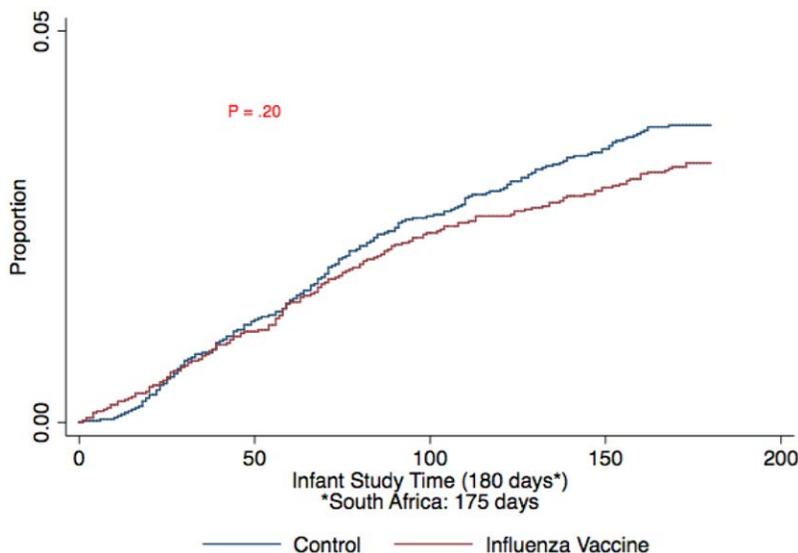
**FIGURE 2.** Kaplan-Meier time-to-severe infant pneumonia. [full color online]

## 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, 200 pregnant women need to be vaccinated. In comparison, the estimated NNV for PCV 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 before pneumococcal infection showed higher mortality rates compared with 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 epidemiologic 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 2-by-2 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 PCV group compared with 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 20% 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, because of varying disease burden and heterogeneity in VE. 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.

## CONCLUSIONS

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.

## ACKNOWLEDGMENTS

*MD; Samba Sow, MD MS; Milagritos Tapia, MD; Boubou Tamboura, PharmD; Ibrahim Teguete, MD; Sharon Tennant, PhD, Awa Traore, PharmD; and John Treanor, MD. Nepal: Janet A. Englund, MD; Joanne Katz, ScD; Subarna K. Khatry, MD; Jane Kuypers, PhD; Steven C. LeClerq, MPH; Luke C. Mullany, PhD; Laxman Shrestha, MD; Mark C. Steinhoff, MD; and James M. Tielsch, PhD. South Africa: Peter V. Adrian, PhD; Clare L. Cutland, MD; Andrea Hugo, MD; Stephanie Jones, MD; Locadiah Kuwanda, MSc; Keith P. Klugman, MD, PhD; Shabir A. Madhi, MD, PhD; Kathleen M. Neuzil, MD; Nadia van Niekerk, BTech; Marta C. Nunes, PhD; Justin R. Ortiz, MD; Eric A.F. Simões, MD; Florette Treurnicht, PhD; Marietjie Venter, PhD; Avy Violari, MD; and Adriana Weinberg, MD.*

## REFERENCES

1. Mackenzie GA, Plumb ID, Sambou S, et al. Monitoring the introduction of pneumococcal conjugate vaccines into West Africa: design and implementation of a population-based surveillance system. *PLoS Med*. 2012;9:e1001161.

2. Berg AS, Inchley CS, Aase A, et al. Etiology of pneumonia in a pediatric population with high pneumococcal vaccine coverage: a prospective study. *Pediatr Infect Dis J*. 2016;35:e69–e75.

3. Klugman KP, Chien YW, Madhi SA. Pneumococcal pneumonia and influenza: a deadly combination. *Vaccine*. 2009;27 (Suppl 3):C9–C14.

4. Brundage JF, Shanks GD. Deaths from bacterial pneumonia during 1918-19 influenza pandemic. *Emerg Infect Dis*. 2008;14:1193–1199.

5. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med*. 2008;359:1555–1564.

6. Madhi SA, Cutland CL, Kuwanda L, et al; Maternal Flu Trial (Matflu) Team. Influenza vaccination of pregnant women and protection of their infants. *N Engl J Med*. 2014;371:918–931.

7. Tapia MD, Sow SO, Tamboura B, et al. Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial. *Lancet Infect Dis*. 2016;16:1026–1035.

8. Steinhoff MC, Katz J, Englund JA, et al. Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial. *Lancet Infect Dis*. 2017;17:981–989.

9. Services DoH. *Annual Report*. Teku, Kathmandu: Government of Nepal Ministry of Health and Population; 2015.

10. Walker CL, Rudan I, Liu L, et al. Global burden of childhood pneumonia and diarrhoea. *Lancet*. 2013;381:1405–1416.

11. Cohen C, Walaza S, Moyes J, et al. Epidemiology of viral-associated acute lower respiratory tract infection among children <5 years of age in a high HIV prevalence setting, South Africa, 2009-2012. *Pediatr Infect Dis J*. 2015;34:66–72.

12. Omer SB, Richards JL, Madhi SA, et al; BMGF Supported Maternal Influenza Immunization Trials Investigators Group. Three randomized trials of maternal influenza immunization in Mali, Nepal, and South Africa: methods and expectations. *Vaccine*. 2015;33:3801–3812.

13. Nunes MC, Cutland CL, Jones S, et al. Efficacy of maternal influenza vaccination against all-cause lower respiratory tract infection hospitalizations in young infants: Results from a randomized controlled trial. *Clin Infect Dis*. 2017.

14. Cutts FT, Zaman SM, Enwere G, et al; Gambian Pneumococcal Vaccine Trial Group. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet*. 2005;365:1139–1146.

15. World Health Organization. *Vaccines and Biologicals: WHO Vaccine-Preventable Diseases: Monitoring System: 2017 Global Summary*. Geneva, Switzerland: World Health Organization; 2017.

16. McCullers JA, Rehg JE. Lethal synergism between influenza virus and Streptococcus pneumoniae: characterization of a mouse model and the role of platelet-activating factor receptor. *J Infect Dis*. 2002;186:341–350.

17. Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon-gamma during recovery from influenza infection. *Nat Med*. 2008;14:558–564.

18. Smillie WG, Warnock GH, White HJ. A study of a type I pneumococcus epidemic at the state hospital at Worcester, Mass. *Am J Public Health Nations Health*. 1938;28:293–302.

19. O'Brien KL, Walters MI, Sellman J, et al. Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. *Clin Infect Dis*. 2000;30:784–789.

20. Omer SB, Zaman K, Roy E, et al. Combined effects of antenatal receipt of influenza vaccine by mothers and pneumococcal conjugate vaccine receipt by infants: results from a randomized, blinded, controlled trial. *J Infect Dis*. 2013;207:1144–1147.

21. van Santen KL, Bednarczyk RA, Adjaye-Gbewonyo D, et al. Effectiveness of pneumococcal conjugate vaccine in infants by maternal influenza vaccination status. *Pediatr Infect Dis J*. 2013;32:1180–1184.