The Pediatric Infectious Disease Journal Publish Ahead of Print

DOI: 10.1097/INF.0000000000001914

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[a, b, c, d], Dayna R. Clark, MPH[b], Anushka R. Aqil, MPH[a], Milagritos D. Tapia, MD[e, f], Marta C. Nunes, PhD[g, h], Naoko Kozuki, PhD[i], Mark C. Steinhoff, MD[i, j], Shabir A. Madhi, PhD[g, h, k], and Niteen Wairagkar, MD[l], for BMGF Supported Maternal Influenza Immunization Trials Investigators Group.

Corresponding Author: Saad B. Omer, somer@emory.edu, Hubert Department of Global Health, CNR 7017, Rollins School of Public Health, Emory University, 1518 Clifton Rd NE, Atlanta, GA 30322, USA

Abbreviated Title: Maternal Flu Immunization and Prevention of Severe Pneumonia

Running Head: Maternal Flu Immunization and Prevention of Pneumonia

[a] Hubert Department of Global Health, Emory University Rollins School of Public Health, Atlanta, GA, USA

[b] Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, USA

[c] Emory Vaccine Center, Atlanta, GA, USA

[d] Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA, USA

[e] Centre pour le Développement des Vaccins, Bamako, Mali

[f] University of Maryland School of Medicine, Center for Vaccine Development, Baltimore, MD, USA

[g] Medical Research Council: Respiratory and Meningeal Pathogens Research Unit, University of the Witwatersrand, Johannesburg, South Africa.

[h] Department of Science and Technology—National Research Foundation, Vaccine-Preventable Diseases, Johannesburg, South Africa

[i] Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

[j] Cincinnati Children's Hospital Global Health Center, Cincinnati, OH, USA

[k] National Institute for Communicable Diseases, The National Health Laboratory Service, Centre for Vaccines and Immunology, Johannesburg, South Africa

[l] Bill & Melinda Gates Foundation, Seattle, WA, USA

Acknowledgement: The three trials in Mali, South Africa, and Nepal as well as this pooled analysis were funded by the Bill & Melinda Gates Foundation. This pooled analysis received research funding from the Bill & Melinda Gates Foundation. Dr. Omer and Ms. Clark serve as consultants to the Bill & Melinda Gates Foundation and received compensation for these services. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies.

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 *Hemophilus 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 ≥ 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