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Review

Three randomized trials of maternal influenza immunization in Mali, Nepal, and South Africa: Methods and expectations

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ABSTRACT

Influenza infection in pregnancy can have adverse impacts on maternal, fetal, and infant outcomes. Influenza vaccination in pregnancy is an appealing strategy to protect pregnant women and their infants. The Bill & Melinda Gates Foundation is supporting three large, randomized trials in Nepal, Mali, and South Africa evaluating the efficacy and safety of maternal immunization to prevent influenza disease in pregnant women and their infants <6 months of age. Results from these individual studies are expected in 2014 and 2015. While the results from the three maternal immunization trials are likely to strengthen the evidence base regarding the impact of influenza immunization in pregnancy, expectations for these results should be realistic. For example, evidence from previous influenza vaccine studies – conducted in general, non-pregnant populations – suggests substantial geographic and year-to-year variability in influenza incidence and vaccine efficacy/effectiveness. Since the evidence generated from the three maternal influenza immunization trials will be complementary, in this paper we present a side-by-side description of the three studies as well as the similarities and differences between these trials in terms of study location, design, outcome evaluation, and laboratory and epidemiological methods. We also describe the likely remaining knowledge gap after the results from these trials become available along with a description of the analyses that will be conducted when the results from these individual data are pooled. Moreover, we highlight that additional research on logistics of seasonal influenza vaccine supply, surveillance and strain matching, and optimal delivery strategies for pregnant women will be important for informing global policy related to maternal influenza immunization.

1. Introduction

Influenza infection in pregnancy can adversely impact maternal, fetal, and infant outcomes [1–7]. While pregnant women tend to be infected with the influenza virus at similar rates as non-pregnant women of similar socio-demographic characteristics, pregnancy increases their likelihood of adverse outcomes after influenza infection. There are physiological changes in pregnancy such as decreased lung capacity, lower tidal volume, and high cardiac output that could play a role in increasing pregnant women's vulnerability to adverse outcomes after influenza infection [8,9]. More importantly, there are immunological changes in pregnancy, such as Th1 to Th2 shift and attenuated cell mediated immunity that modify a pregnant woman's

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ability to respond to certain infections—particularly viral infections [10,11].

The Bill & Melinda Gates Foundation (BMGF) is supporting three large, randomized trials evaluating the efficacy and safety of maternal immunization to prevent maternal and young–infant (<6 months of age) influenza disease in Nepal, Mali, and South Africa [10]. The primary results from the South Africa trial have been published [11] and results from the other two trials are expected in 2014/2015 and will advance decisions on influenza vaccine introduction for pregnant women in resource-limited settings. Furthermore, a pooled analysis of data from these trials will be valuable for understanding the benefits of and building the evidence base for this intervention, particularly for outcomes for which individual trials may not have been powered.

Since the evidence generated from these trials will be complementary, in this paper we present a side-by-side description, as well as similarities and differences between these trials in terms of study location, design, outcome evaluation, and laboratory and epidemiological methods. We discuss the expectations from these trials and describe the outcomes selected for pooled analyses, the process and criteria for selecting these analyses, and statistical methods to be used in the analyses. This will serve as a resource for interpreting findings from the three BMGF-sponsored trials as the results from these studies become available in the coming years.

2. Rationale for conducting maternal influenza immunization trials

Influenza vaccination in pregnancy is an appealing strategy to protect pregnant women and their young–infants. There have been several recent developments in the field of maternal influenza immunization. The World Health Organization's Strategic Advisory Group of Experts on Immunization has concluded that vaccination of pregnant women is safe [12]. Furthermore, in a randomized controlled trial in Bangladesh, administration of inactivated influenza vaccine in the third trimester of pregnancy was associated with reduction of confirmed influenza (using rapid ELISA test) by 63% among infants younger than 6 months of age [13]. Maternal influenza immunization has also been associated with protection against adverse birth outcomes such as prematurity and small for gestational age birth in observational studies and post-hoc analyses of trial data [3,14], although this finding has not been consistently observed by others [15] (particularly in studies that do not account for influenza infection/circulation). Consequently, whereas these advances are promising, many questions remain.

While the Bangladesh trial was a significant milestone for developing an evidence base for maternal influenza immunization, it had some limitations. For example, this trial was conducted during a single influenza season over an 11 month period. Since the epidemiology of influenza varies substantially by geography and season, the findings from the Bangladesh trial need to be replicated in other settings and over multiple seasons. Another limitation of this trial is that the efficacy of maternal influenza vaccination was computed in comparison with the pneumococcal polysaccharide vaccine (PPSV). While PPSV served as the comparison group for the influenza vaccine analysis, PPSV was the main intervention when the trial was initiated. PPSV could have affected the risk of non-laboratory-confirmed outcomes such as influenza-like illness, which could have impacted on the true efficacy of maternal influenza immunization against some outcomes. Moreover, the association between maternal influenza immunization and birth outcomes was evaluated post hoc in the Bangladesh trial and has never been evaluated using a priori outcomes in a randomized controlled trial.

3. Rationale for pooled analysis

We sought to conduct a pooled analysis of data from the three trials to further build an evidence base for maternal immunization interventions. While the three trial sites will provide necessary data as it relates to maternal immunization, by pooling the data, we will be able to examine various outcomes for which individual trials may not have been powered. Pooled analysis, often described as meta-analysis of individual level data, has several advantages over "traditional" meta-analysis (i.e. meta-analysis based on summary estimates). In contrast with traditional meta-analysis, pooled analysis allows for better standardization of analytical variables, more robust confounder control, and greater ability to evaluate heterogeneity and effect modification. Therefore, given that we have access to individual level data from the three trials, we opted for the pooled analysis approach rather than using the traditional group-level meta-analysis to synthesize information from these trials.

4. Trial descriptions

A side-by-side description of the three trials is provided in Tables 2–4 and supplement; a comparison of maternal mortality ratios and infant mortality rates is also provided in Table 1. Briefly, all three are randomized, controlled, blinded trials. Enrollment occurred from mid-September 2011 to mid-April 2013 in Mali, mid-April 2011 to mid-April 2013 in Nepal, and March 2011 to August 2011 and March 2012 to July 2012 in South Africa. The enrollment was targeted to coincide with the influenza season in South Africa; whereas, the other two sites enrolled and vaccinated participating women year round. In Nepal, multiple peaks of influenza activity were observed in December 2011, August–October 2012, May 2013, June–August 2013, March–April 2014, July–September 2014, and February–March 2015. In South Africa, the 2011 season had 2 distinct peaks. The first peak, starting the week of 13 June which was followed by a second peak, on the week of 26 September; 2012 season had a peak starting on the week of 20 August. In Mali, peaks were observed in September/October and in February from 2010 to 2014.

In Mali, where there is no formal influenza vaccination policy, pregnant women receiving prenatal care at six referral centers and community health centers in Bamako were offered enrollment. In Nepal, where there is also no formal influenza vaccination policy, women who were or who became pregnant in 9 Village Development Committees in Sarlahi District in southern Nepal were included; the participants were all identified by baseline household surveys. In South Africa, where there has been a national campaign for influenza vaccination of pregnant women since 2010, enrollment was conducted among women accessing prenatal care at Chris Hani-Baragwanath Hospital or at one of four community-based antenatal clinics in Soweto region in Johannesburg. Within the South African program, separate cohorts of HIV-uninfected women ($n = 2108$) and HIV-infected women ($n = 180$) were enrolled. Only the HIV-uninfected cohort is included in the proposed pooled analyses, as the primary objective of the HIV-infected cohort was evaluation of safety and immunogenicity (rather than efficacy) of influenza vaccine. Women were enrolled and vaccinated at ≥28 weeks of gestation in Mali, at 17–34 weeks of gestation in Nepal, and at ≥20 to <36 weeks of gestation in South Africa. Study subjects were followed from enrollment through delivery and approximately 6 months of infant age at all three sites (South Africa defined the follow up period as 24 weeks postpartum; whereas the other two sites defined it as 6 months). Details of differences in the eligibility criteria are described in Table 2. Moreover, all three trials individually randomized the enrolled women with a 1:1 randomization ratio using block randomization