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Translating vaccine policy into action: A report from the Bill & Melinda Gates Foundation Consultation on the prevention of maternal and early infant influenza in resource-limited settings

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ABSTRACT

Immunization of pregnant women against influenza is a promising strategy to protect the mother, fetus, and young infant from influenza-related diseases. The burden of influenza during pregnancy, the vaccine immunogenicity during this period, and the robust influenza vaccine safety database underpin recommendations that all pregnant women receive the vaccine to decrease complications of influenza disease during their pregnancies. Recent data also support maternal immunization for the additional purpose of preventing disease in the infant during the first six months of life.

In April 2012, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization recommended revisions to the WHO position paper on influenza vaccines. For the first time, SAGE recommended pregnant women should be made the highest priority for inactivated seasonal influenza vaccination. However, the variable maternal influenza vaccination coverage in countries with pre-existing maternal influenza vaccine recommendations underscores the need to understand and to address the discrepancy between recommendations and implementation success.

We present the outcome of a multi-stakeholder expert consultation on inactivated influenza vaccination in pregnancy. The creation and implementation of vaccine policies and regulations require substantial resources and capacity. As with all public health interventions, the existence of perceived and real risks of vaccination will necessitate effective and transparent risk communication. Potential risk allocation and sharing mechanisms should be addressed by governments, vaccine manufacturers, and other stakeholders. In resource-limited settings, vaccine-related issues concerning supply, formulation, regulation, evidence evaluation, distribution, cost-utility, and post-marketing safety surveillance need to be addressed. Lessons can be learned from the Maternal and Neonatal Tetanus Elimination Initiative as well as efforts to increase vaccine coverage among pregnant women during the 2009 influenza pandemic. We conclude with an analysis of data gaps and necessary activities to facilitate implementation of maternal influenza immunization programs in resource-limited settings.

1. Introduction

The burden of influenza in pregnant women and young infants and the efficacy of maternal vaccination in preventing disease in infants younger than six months of age indicate that influenza vaccination can impact disease in two high-risk groups with one vaccine dose delivered during pregnancy [1]. In 2011, the Bill & Melinda Gates Foundation convened an international consultation of multidisciplinary global health experts to consider the potential for maternal influenza immunization in resource-limited settings (Online Supplemental Table 1). This report summarizes the expert presentations and discussions regarding inactivated influenza vaccination of pregnant women. It also presents the outcome of plenary sessions to identify data gaps and necessary activities to facilitate implementation of maternal influenza immunization programs in resource-limited settings.

2. Influenza burden

The substantial risk of severe influenza disease to pregnant women is well recognized. Increased risk of death was documented among pregnant women during the 1918 and 1957 pandemics [2]. Excess disease also has been noted among pregnant women during interpandemic periods, particularly in the third trimester [2,3]. Considerable clinical and epidemiological data collected during the 2009 H1N1 pandemic support the earlier findings that pregnant and postpartum women are at high risk for severe complications of influenza illness [2,4–8]. While most morbidity data are from temperate, developed settings, they provide the underpinning for

Abbreviations: AEFI, adverse event following immunization; ALRI, acute lower respiratory infections; EMA, European Medicines Agency; EPI, Expanded Programme on Immunization; FDA, United States Food and Drug Administration; GACVS, WHO Global Advisory Committee on Vaccine Safety; H1N1, 2009 pandemic influenza A (H1N1); MNCH, Maternal, Newborn, and Child Health; MNT, Maternal and Neonatal Tetanus; NITAG, national immunization technical advisory groups; NRA, national regulatory authorities; PAHO, Pan American Health Organization; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; SAGE, WHO Strategic Advisory Group of Experts on Immunization; SGA, small for gestational age; SIVAC, Supporting Independent Immunization and Vaccine Advisory Committees Initiative; TIV, trivalent inactivated influenza vaccine; TT, tetanus-toxoid (TT) - containing vaccines; VICP, US National Vaccine Injury Compensation Program.

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recommendations that pregnant women represent a high priority target group for inactivated seasonal influenza vaccination [9].

The substantial burden of influenza disease in young children has been established from many surveillance studies performed in high-resource settings [2,3,10]. Several recent pneumonia etiology studies from resource-limited settings have reported high proportions of children younger than five years of age with influenza-associated acute lower respiratory infections (ALRI) [11–13]. A recent systematic review and meta-analysis estimates the global burden of severe influenza-associated ALRI [14]. The study reports that 99% of related deaths among children younger than five years of age occur in resource-limited settings, and the incidence of severe ALRI among children younger than one year of age appears to be greater in low-resource as compared to high-resource settings [14]. Specific data on the burden of influenza in children younger than six months of age (the period during which maternal antibodies are present in greatest concentrations) remain limited [2,3,15,16].

3. Vaccine safety, immunogenicity, and efficacy

Several reviews of inactivated influenza vaccine in pregnancy have been published recently [1,7,17–22]. The safety profiles of seasonal, trivalent inactivated influenza vaccine (TIV) and pandemic 2009 influenza A (H1N1) vaccine (with and without adjuvant) during pregnancy are comparable to those in non-pregnant adults [1,18,23–26]. Reported maternal reactogenicity is mostly mild and self-limited, and there has been no evidence of teratogenicity or adverse pregnancy outcomes.

Despite the burden of influenza disease during pregnancy, no vaccine effectiveness studies of TIV in pregnant women have assessed laboratory-confirmed influenza outcomes among vaccine recipients [1]. However, multiple studies have shown the efficacy of TIV in young and middle-aged adult women, and TIV vaccine immunogenicity in pregnant women is similar to that in non-pregnant women [1,3,17,27,28]. One randomized clinical trial in Bangladesh found that women who received TIV in pregnancy were 36% less likely to develop febrile respiratory illness [29]. Several maternal influenza vaccine trials with laboratory-confirmed endpoints among the women and their infants are planned or are ongoing, including trials funded by the Gates Foundation in Mali, Nepal, and South Africa [30].

Observational studies have found variable benefit to newborns of vaccination of their mothers during pregnancy [1,31–35]. However, all prospective studies with laboratory-confirmed endpoints have shown benefit of maternal vaccination against influenza disease in young infants [29,33,35]. The effectiveness of maternal immunization to prevent symptomatic, laboratory-confirmed influenza virus infection in infants was 41% in US Native Americans and 69% in Bangladesh [29,33]. The vaccine effectiveness of maternal immunization to prevent infant influenza-associated hospitalization was 45% in the US New Vaccine Surveillance Network and 92% in a single center study in the United States [31,35].

Recent data suggest that maternal influenza immunization may have beneficial fetal effects [10]. In a post hoc analysis of the Bangladesh clinical trial data, pregnant women who received TIV had a 70% decrease in the risk of small for gestational age (SGA) births as compared to women who received a pneumococcal polysaccharide vaccine (PPV) [36]. This finding was supported by observational studies in North America that also found maternal TIV to be associated with both decreased preterm births and decreased SGA births [37,38], as well as two other studies that found maternal influenza virus infection was associated with decreased birthweight [39,40]. An additional potential benefit of maternal TIV may include synergy with pneumococcal conjugate vaccine (PCV). Investigators from the Bangladesh trial have reported a decrease in acute respiratory infections among infants who had received PCV vaccine and whose mothers received TIV when compared to other infants who had received different maternal/infant vaccine combinations [41].

4. Global maternal influenza vaccine policy

In a 2005 position paper, WHO encouraged countries to prioritize influenza vaccination for all pregnant women during the influenza season, as defined by national data and capacities [42]. For the 2009 H1N1 influenza pandemic, WHO deferred to member states to prioritize their own country-specific high-risk groups, although the WHO Strategic Advisory Group of Experts (SAGE) recommended that countries consider pregnant women among its vaccination priority populations [43]. In April 2012, SAGE recommended revisions to the current policy as described in the WHO 2005 position paper on influenza vaccines [9,42]. For the first time, SAGE recommended that pregnant women represent the most important of the risk groups for receipt of inactivated seasonal influenza vaccination [9]. These recommendations are based on "compelling evidence of substantial risk of severe disease in this group and evidence that seasonal influenza vaccine is safe and effective in preventing disease in pregnant women as well as their young infants, in whom disease burden is also high [9]". To date, WHO has made no recommendation for timing (trimester) of influenza vaccine during pregnancy. An update of the WHO Position Paper on use of influenza vaccine (including use during pregnancy) is expected later in 2012. National maternal influenza immunization recommendations exist for some countries [3,44]. However many other countries have not yet addressed use of influenza vaccine in pregnancy within national immunization policies. Notwithstanding the presence of national maternal immunization recommendations, vaccine coverage is often below goals in high-resource and low-resource countries [44–46].

Despite existing recommendations for the use of some vaccines during pregnancy, SAGE has noted that pregnancy was a commonly cited contraindication to a wide range of vaccines, but indicated that in many cases this was precautionary and not evidence-based [47]. SAGE therefore requested that the WHO Global Advisory Committee on Vaccine Safety (GACVS) review the safety of vaccines in pregnancy [47], and this work is ongoing. Additional efforts to address other barriers to maternal immunization are discussed below.

5. WHO vaccine prequalification

According to the WHO, vaccine prequalification is "a service to UNICEF and other UN agencies that purchase vaccines to determine the acceptability of vaccines from different sources" [48]. This process of vaccine prequalification provides independent opinion and advice on the quality, safety, and efficacy of vaccines [48]. Prequalification "ensures that candidate vaccines are suitable for the target population" and meet the needs of programs, and the process ensures "continuing compliance with specifications and established standards of quality" [48]. There are several prequalified influenza vaccines to date [49]. While not a regulatory procedure, prequalification requires that a vaccine be regulated by at least one national regulatory authority.

Package inserts for prequalified influenza vaccines differ with regards to statements of fetal risk, depending on whether animal reproduction toxicity studies have been performed for the particular product (Table 1). The use of influenza vaccines during pregnancy is addressed in the package inserts which recommend use when "needed". However, package inserts do not specify the