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Report of the WHO technical consultation on the effect of maternal influenza and influenza vaccination on the developing fetus: Montreal, Canada, September 30–October 1, 2015

Deshayne B. Fell[a,b], **Zulfiqar A. Bhutta**[c], **Jennifer A. Hutcheon**[d], **Ruth A. Karron**[e], **Marian Knight**[f], **Michael S. Kramer**[g], **Arnold S. Monto**[h], **Geeta K. Swamy**[i], **Justin R. Ortiz**[j,*], **David A. Savitz**[k]

[a]School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Canada [b]Children's Hospital of Eastern Ontario (CHEO) Research Institute, 401 Smyth Road, Ottawa, ON K1H 8L1, Canada [c]Centre for Global Child Health, Hospital for Sick Children, 525 University Avenue, Suite 702, Toronto, ON M5G 2L3, Canada [d]Department of Obstetrics & Gynaecology, University of British Columbia, Shaughnessy Building C408A, 4500 Oak Street, Vancouver, BC V6N 3N1, Canada [e]Center for Immunization Research, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA [f]National Perinatal Epidemiology Unit, University of Oxford, Old Road Campus, Oxford OX3 7LF, United Kingdom [g]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, 4018 Ste-Catherine St W, Room K-116, Westmount, QC H3Z 1P2, Canada [h]Department of Epidemiology, University of Michigan School of Public Health, 1415 Washington Heights, 1700 SPH I, Ann Arbor, MI 48109-2029, USA [i]Department of Obstetrics and Gynecology, Duke University, 2608 Erwin Rd, Suite 210, Durham, NC 27710, USA [j]Initiative for Vaccine Research, World Health Organization, 20, Avenue Appia, CH-1211 Geneva 27, Switzerland [k]Departments of Epidemiology and Obstetrics and Gynecology, Brown University, 47 George Street, Providence, RI 02912, USA

Abstract

In 2012, the World Health Organization (WHO) released a position paper on influenza vaccination recommending that pregnant women have the highest priority for seasonal vaccination in countries where the initiation or expansion of influenza immunization programs is under consideration. Although the primary goal of the WHO recommendation is to prevent influenza illness in pregnant women, the potential benefits of maternal immunization in protecting young infants are also recognized. The extent to which maternal influenza vaccination may prevent adverse birth

*Corresponding author. ortizj@who.int (J.R. Ortiz).

Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.03.056.

outcomes such as preterm birth or small-for-gestational-age birth, however, is unclear as available studies are in disagreement.

To inform WHO about the empirical evidence relating to possible benefits of influenza vaccination on birth outcomes, a consultation of experts was held in Montreal, Canada, September 30–October 1, 2015. Presentations and discussions covered a broad range of issues, including influenza virus infection during pregnancy and its effect on the health of the mother and the fetus, possible biological mechanisms for adverse birth outcomes following maternal influenza illness, evidence on birth outcomes following influenza illness during pregnancy, evidence from both observational studies and randomized controlled trials on birth outcomes following influenza vaccination of pregnant women, and methodological issues. This report provides an overview of the presentations, discussions and conclusions.

Keywords

Influenza vaccination; Pregnancy; Preterm birth; Fetal growth; Stillbirth

1. Background and meeting objectives

High-quality evidence from randomized controlled trials (RCTs) has shown that the benefits of immunization during pregnancy are two-fold: vaccination prevents influenza illness in mothers [1–3] and their young infants [2,3]. Some observational studies suggest additional value for maternal influenza immunization programs [4–6] through a reduced risk of adverse birth outcomes such as preterm birth, small-for-gestational-age (SGA) birth, or stillbirth [7,8]. However, the evidence for these additional benefits is inconsistent and is based largely on observational studies with many important methodological limitations [4]. Clear evidence of fetal benefits from maternal influenza immunization would have important implications for immunization programs in lower resourced settings. In 2013, Gavi, The Vaccine Alliance conducted a technical review of potential health impacts of maternal influenza immunization programs in low-income countries [9]. This review predicted that the number of infant deaths averted could increase by 4-fold if vaccination reduced preterm birth by 17%, as was suggested by the single observational study [10] included in their impact model. The investment, however, was not pursued, largely due to inadequate data on the burden of influenza disease, including studies assessing adverse birth outcomes following influenza during pregnancy [9,11].

In this meeting report, we highlight presentations and discussions from a consultation of subject matter experts convened to inform the World Health Organization (WHO) about the empirical evidence of possible benefits of maternal influenza vaccination on birth outcomes. The meeting was held in Montreal, Canada, from September 30–October 1, 2015 with experts from a wide variety of health disciplines (see Appendix A for the meeting agenda and Appendix B for the participant list). The overall aim of the meeting was to review the scientific evidence bearing on the effect of maternal influenza vaccination on birth outcomes, with specific focus on the epidemiology of adverse birth outcomes, relationship between maternal influenza disease during pregnancy and birth outcomes, current evidence on birth outcomes from observational studies and randomized controlled trials (RCTs) of

influenza vaccine and epidemiological plausibility of protective effects of influenza vaccine on birth outcomes reported in some previous studies.

2. Epidemiology of adverse birth outcomes

Owing to the varied backgrounds of meeting participants, several initial presentations provided an overview of the epidemiology of adverse birth outcomes. The scope of the meeting primarily focused on the three outcomes that have been most extensively reported in influenza vaccination studies: preterm birth, SGA birth and stillbirth. Preterm birth, defined as birth prior to 37 weeks of gestation, is a leading cause of neonatal and childhood mortality worldwide [12]. In 2010, an estimated 11% of live births were born at preterm gestation, though regional rates varied from 7.2% in Eastern Asia to 13.6% in Southeastern Asia, with some countries in sub-Saharan Africa experiencing rates as high as 18% [12] (Table 1). Preterm birth has complex, multifactorial pathophysiology [13] involving medical, genetic, social and environmental factors [14]. The most frequent risk factors for spontaneous preterm birth in high-income settings include genitourinary tract infection, gestational hypertension or pre-eclampsia and uterine overdistention due to multi-fetal gestation, while young maternal age, short inter-pregnancy interval and low maternal body mass index are the most common risk factors in low-resource settings [14,15].

SGA birth is most commonly defined as a birth weight less than the 10th percentile for sex and gestational age. By definition, therefore, the global prevalence using local growth standards would be expected to be 10%. However, when a common reference standard is used, the global distribution of SGA infants varies widely [16], with the highest burden in absolute number and prevalence occurring in South Asia (44.5%) [17]. In low- and high-income settings, maternal smoking, low maternal body mass index, gestational hypertension or pre-eclampsia and low gestational weight gain are leading risk factors for SGA. Other major risk factors in rural low-resource settings include maternal short stature and malaria [15]. The use of birth weight (or low birth weight, i.e., <2500 g) alone as a study outcome is discouraged, since infant birth weight is highly dependent on gestational duration [18].

Various stillbirth definitions are used around the world [19–21], making direct comparisons across countries difficult. Using the WHO definition of stillbirth recommended for international comparisons (≥28 completed weeks' gestation), the stillbirth rate in 2015 ranged from an estimated 3.4 per 1000 total births in high-income regions to 28.7 per 1000 total births in sub-Saharan Africa (Table 1) [22]. Stillbirth can result from intrauterine infection, maternal obstetrical conditions or fetal conditions, but the most common precursors, accounting for about 70% of all stillbirths, are intrapartum (labor) complications, placental disease and structural congenital anomalies [23,24]. Stillbirth is challenging to study, given discrepant definitions and classification systems [20] and the lack of high-quality data, or indeed any data, in many settings [25]. Consequently, most stillbirths do not have a well-defined cause, particularly in low-resource settings [20].

3. Influenza virus infection during pregnancy

3.1. Risks of severe influenza outcomes among pregnant women

Complex pregnancy-induced physical and physiological changes [26], including immune system alterations, are thought to render pregnant women more susceptible to severe illness once infected with influenza virus [27–30]. Numerous descriptive reports from influenza pandemics documenting influenza-related morbidity and mortality in pregnant women [31–35] have contributed to the recognition of pregnancy as a risk factor for severe influenza illness. A recent systematic review assessed whether pregnant women are at higher risk for severe influenza-associated health outcomes compared with non-pregnant women of reproductive age [36]. The review was carried out as part of the WHO Taskforce to Evaluate Influenza Data to Inform Vaccine Impact and Economic Modelling, a working group convened to inform efforts by the WHO Initiative for Vaccine Research to promote evidence-based implementation research for influenza vaccine programs [37]. In comparative observational studies included in the review, pregnant women had a higher risk of laboratory-confirmed influenza (LCI) hospitalization than non-pregnant women (pooled odds ratio [OR] 2.94; 95% confidence interval [CI]: 1.58–5.47), but no differences were seen for severe outcomes such as LCI intensive care unit admission or death. The authors concluded that pregnant women may be hospitalized at a higher rate than non-pregnant women of reproductive age on a precautionary basis, since severe influenza outcomes did not differ between the two groups, although the low quality of evidence across studies [38] was acknowledged as a limitation of the review. A list of study quality issues and evidence gaps identified by the review is provided in Table 2.

3.2. Influenza virus infection and risks to the fetus

High rates of pregnancy loss and preterm delivery were documented in case series from the 1918–1919 influenza pandemic, particularly among influenza-infected pregnant women who developed secondary pneumonia [32]. Increases in other adverse outcomes such birth defects have also been reported in case series from 20th-century influenza pandemics [39], but not consistently [40]. With few exceptions [41,42], descriptive studies from the influenza A (H1N1) pandemic in 2009 reported increased rates of adverse birth outcomes among infected pregnant women, especially among hospitalized cases [34,43–45]. However, the absence of a comparison group in these studies limits their ability to causally attribute adverse birth outcomes to influenza disease [46]. Moreover, many of the reports were limited to information collected at the time of an antepartum hospital admission and lacked information on the final outcome of the pregnancies delivered at a later time [34].

In early 2015, the WHO Taskforce assessing influenza immunization during pregnancy [37] initiated a systematic review of influenza-associated risks of preterm birth, SGA birth and fetal death [47]. The review identified 21 comparative studies of adverse birth outcomes and maternal influenza disease. The quality of the evidence was considered low to very low for all outcomes, owing to the limited number of studies (particularly for SGA birth and fetal death), inconsistency of results and concerns about ascertainment of influenza disease. A small number of higher-quality studies suggested that severe 2009 pandemic H1N1 (pH1N1) influenza disease was associated with an increased risk of preterm birth [48,49], but no

association was found for mild-to-moderate 2009 pH1N1 influenza [50–52], nor for seasonal influenza [51,53]. Five studies of SGA birth suggested a small increase in risk associated with influenza virus infection (pooled OR: 1.24; 95% CI: 0.96–1.59) [47]. The highest quality evidence for fetal death outcomes (miscarriage and/or stillbirth) was limited to two studies, both of which reported a significantly increased risk of fetal death following maternal 2009 pH1N1 influenza disease [48,50]. The remaining studies were considered at high risk of bias [54] or had too few fetal deaths for meaningful interpretation. The systematic review found little evidence that mild maternal influenza illness was associated with adverse birth outcomes but acknowledged many limitations in the available evidence (Table 2).

3.3. Possible biological mechanisms for adverse birth outcomes following maternal influenza during pregnancy

Several potential pathways through which maternal influenza disease could lead to adverse birth outcomes were discussed: direct viral injury to the placenta or fetus, maternal immunological responses affecting placental function or temperature regulation and medical intervention. Human fetal membranes act as defensive barriers to protect the developing fetus against infectious agents [55]. Although maternal influenza viremia with transplacental transfer to fetal tissues has been documented in human cases of severe infection or highly pathogenic strains [56–58] and in lab studies [59], direct viral infection of the fetus is considered rare [55,60,61]. The fetal membranes additionally play an important role in the regulation of processes that initiate normal parturition through cytokine production [55]. Systemic maternal infection elicits inflammatory responses such as elevated proinflammatory cytokine levels [62], a known pathway to spontaneous preterm birth [20,63] and the main hypothesized mechanism by which influenza virus infection could lead to spontaneous preterm birth [56,60,61,64,65]. Another immune response, transient maternal hyperthermia [60,66] has also been associated with an increased risk of congenital anomalies [67]. Other medical interventions, such as pharmacologic therapies (e.g., antiviral or antipyretic medications), could also theoretically be associated with some adverse birth outcomes, but distinguishing between potential pathogenic effects of the influenza virus and iatrogenic effects of medications used to manage the infection is complex and requires further study [68]. Infection-related maternal inflammation and hyperthermia can also be elicited by other pathogens, making it unclear whether the influenza virus itself, or its sequelae (e.g., associated symptoms, secondary infections), or both are harmful during pregnancy.

The gestational age at which influenza virus infection occurs is highly relevant when considering possible biological effects of influenza disease. Complex physiological changes that increase with advancing gestation [29] may explain why pregnant women are at highest risk for influenza-related complications during the third trimester [69,70]. From the perspective of birth outcomes, only infection during early pregnancy can plausibly be associated with congenital anomalies or miscarriage; however, for outcomes such as preterm birth, stillbirth or SGA birth, the most susceptible gestational time windows for fetal exposure to maternal influenza are unknown. It is theoretically possible for early pregnancy maternal influenza disease to predispose to a preterm birth or stillbirth at a later gestation,

representing a delayed effect of exposure on outcome. But it is more likely that such adverse birth outcomes are precipitated by an acute effect of influenza infection. Conversely, fetal growth restriction resulting in an SGA birth results from pathological processes that take place over a longer duration of time, making it unlikely that influenza disease would have a short-term acute effect.

4. Observational studies of influenza immunization during pregnancy and birth outcomes

4.1. Current evidence

The results from a systematic review of comparative studies of influenza immunization during pregnancy published up to April 2014 were discussed [7]. The review included 27 studies, 14 of which exclusively evaluated 2009 monovalent pH1N1 vaccines. Three studies of fetal death (at any gestational age) reported non-significant relative protective effect estimates in the range of 0.56–0.79, while four of five studies of early fetal death (<20 weeks' gestation) reported estimates between 0.89 and 1.23 with confidence intervals including the null value [7]. Four of five studies of stillbirth (fetal death at ≥20 weeks' gestation) reported estimates ranging from 0.44 to 0.77, including two with statistically significant results [71,72]. Although heterogeneity prevented meta-analysis of the 19 studies reporting preterm birth, studies generally reported either no association between influenza vaccination and preterm birth or decreased risks, some of which were statistically significant [73–76]. The authors inferred no increased risk of preterm birth or fetal death associated with influenza vaccination in pregnancy but emphasized the need for cautious interpretation of the decreased risks reported by several studies, given important methodological limitations of many of the primary studies.

4.2. Methodological considerations

Meeting participants discussed a number of methodological issues concerning observational studies of influenza vaccination in pregnancy, details of which have been published [4,77,78]. The two most important issues identified were: (i) confounding bias due to a more favorable health profile among pregnant women who select vaccination, and (ii) asymmetry between studies of potential harm and potential benefit of vaccination. In observational studies of influenza vaccination in elderly populations, healthier seniors have been shown to preferentially receive influenza vaccination. This selection makes immunization appear strongly protective against a range of health outcomes to an implausible degree, given influenza-attributable risks for these outcomes [79–82]. Statistically significant risk reductions for non-specific outcomes during time periods with no circulating influenza viruses and during seasons with a poor match between the vaccine and circulating virus have demonstrated the extent of this confounding bias [79–83]. The impact of such bias in the obstetrical population has not been extensively studied, but significantly reduced risks of preterm birth and fetal death reported by some observational studies [7], including some with methodologically strong study designs (e.g., survival analyses with time-varying exposures) and multivariable statistical adjustment [71,84], may implicate similar issues.

The importance of distinguishing between potential harm and benefit of vaccination during pregnancy was stressed [4]. To date, most observational studies of influenza vaccination in pregnancy were designed and analyzed to address the former; yet many of these studies have inferred beneficial effects of vaccination on birth outcomes. When assessing a potential harmful effect of vaccination on birth outcomes, all vaccinated women are at risk from the time of vaccine administration, irrespective of the timing of the influenza season. Conversely, an assessment of potential benefit from influenza vaccination must assume that influenza prevention is on the causal pathway and account for temporal features of influenza circulation [4]. Moreover, any beneficial effect of influenza vaccination can be achieved only among the small subset of women whose influenza illness was prevented by vaccination and in whom influenza illness would otherwise (i.e., counterfactually) have resulted in an adverse birth outcome (Fig. 1). To illustrate using preterm birth as an example, in a population with an 11% baseline risk of preterm birth [12], 5% influenza attack rate [85] and 50% vaccine efficacy [86], influenza illness would be prevented in 2.5% of vaccinated women. Assuming a moderate association between preterm birth and influenza virus infection (e.g., risk ratio [RR] = 1.5), the expected risk ratio for preterm birth comparing vaccinated to unvaccinated women would be 0.99 [77]. To obtain a risk ratio for preterm birth of 0.80 in the overall obstetrical population, similar in magnitude to reports from some observational studies [73–76], influenza virus infection would have to result in at least a 2-fold increase in risk of preterm birth, attack rates would have to be in excess of 20%, and vaccine efficacy would have to be at least 70% [77], conditions that are unlikely to be seen in the overall obstetrical population.

5. Randomized controlled trials of influenza immunization during pregnancy and birth outcomes

In September 2015, when this meeting took place, two published RCTs of influenza immunization during pregnancy were available for review: one from Bangladesh [2] and the other from South Africa [3]. The latter trial was the first of three Bill and Melinda Gates Foundation (BMGF)-funded RCTs to be published on influenza immunization during pregnancy. Results from two additional BMGF-funded RCTs in Mali and Nepal [87] were not yet available and thus were not part of the meeting discussions. Although the primary purpose of the Bangladesh and South Africa trials was to evaluate the efficacy of maternal influenza immunization to prevent influenza illness in mothers and infants, our discussions focused on the relationship between maternal influenza immunization and birth outcomes.

5.1. Bangladesh trial

The first RCT to assess infant protection against laboratory-confirmed influenza virus infection following maternal influenza immunization was conducted in Bangladesh in 2004–2005. This trial randomized 340 pregnant women to receive either trivalent inactivated influenza vaccine (control arm) or pneumococcal polysaccharide vaccine (experimental arm) in the third trimester of pregnancy. Influenza vaccine was efficacious in preventing respiratory illness with any fever in women during the follow-up period, which extended from two weeks post-randomization to 24 weeks post-delivery (vaccine efficacy [VE]: 35.8, 95% CI: 3.7–57.2). Efficacy against maternal respiratory illness with fever above 38 °C was

not statistically significant [2]. Overall, no statistically significant differences were observed in adverse birth outcomes such as SGA birth or preterm birth between the two treatment groups (Table 3) [2]. In post hoc analyses of 116 infants born during the influenza season, however, mean birth weight was significantly increased among infants born to women who received influenza vaccine, compared with those who received pneumococcal polysaccharide vaccine (adjusted mean difference: +190 g, 95% CI: 9–378), while the risk of SGA birth was significantly reduced (adjusted OR: 0.44; 95% CI: 0.19–0.99) [88]. These effects were not observed among 211 infants born when influenza was not circulating.

5.2. South Africa trial

The second published trial, conducted in South Africa in 2011–2012, demonstrated a benefit of influenza vaccination during pregnancy in preventing laboratory-confirmed maternal influenza virus infection between randomization and 24 weeks post-partum [3]. Among the 2116 non-HIV-infected pregnant women randomized to receive either influenza vaccine or placebo, laboratory-confirmed maternal influenza virus infection was significantly reduced (VE: 50.4, 95% CI: 14.5–71.2) [3]. No differences were seen between the treatment groups in mean birth weight, mean gestational age or risk of preterm or SGA birth [3], even after accounting for maternal pregnancy exposure to time periods when influenza virus was circulating (Table 3) [89].

5.3. Discussion of trial results

The group discussion focused on interpretation of trial findings on birth outcomes, as well as potential explanations for the divergence in some findings on birth outcomes between the two published trials. First, unlike therapeutic trials in which all participants have the disease and stand to benefit from the intervention, the expectation in these preventive trials is that any potential beneficial effect of influenza immunization on birth outcomes would occur through prevention of maternal influenza illness during pregnancy. Since the influenza attack rates in these trials were low, even in unimmunized women, and vaccine efficacy in pregnant women was approximately 36–50%, a very large adverse effect of influenza infection on birth outcomes would be required to produce a protective effect of influenza vaccination on birth outcomes in the overall study population. Much of the discussion on this issue revolved around interpreting the 190-g adjusted increase in mean birth weight in the influenza vaccine group (compared with the pneumococcal polysaccharide vaccine group) from the Bangladesh trial. These findings were limited to analysis of the sub-group of 116 infants (58 per treatment group) born during the time period when influenza virus was circulating [88]. For perspective, differences in mean birth weight between smoking and non-smoking mothers are typically around 150–200 g [90], which is of the same order of magnitude as the mean birth weight differences observed between the vaccine groups. Yet, maternal influenza virus infection has not been recognized among the leading risk factors for poor fetal growth, while maternal smoking is one of the strongest known risk factors [90]. Results from the two additional forthcoming BMGF-sponsored clinical trials [87] were recognized as critical for more robust interpretation of possible beneficial effects of influenza immunization on infant birth weight, particularly the Nepal RCT, which had the assessment of birth weight differences as the primary study outcome [87].

Participants also raised general concerns about post hoc analyses. Even when nested within an RCT, analyses of sub-groups defined post hoc are prone to type 1 errors [91]. Moreover, differences in gestational age at vaccination and in the number of days from vaccination to delivery were documented in the Bangladesh trial between the post hoc comparison groups, raising the possibility of confounding bias [88]. On average, influenza-vaccinated women who gave birth during the influenza season were at a slightly more advanced gestation than the pneumococcal-vaccinated women during the same time period, and thus had less gestational time in which to develop influenza-mediated effects on fetal growth. The investigators recognized this and included statistical adjustments for gestational age at immunization and interval from immunization to delivery, but post hoc sub-group testing remains a problem. Stratified analyses by influenza time period were also conducted, but not extensively reported, from the South Africa trial [89].

Finally, several possible explanations for the divergent findings for birth weight between the two published trials were proposed, including local differences in influenza season characteristics or season-specific influenza vaccine components, differences in the comparison groups (active control [2] versus placebo control [3]) and differential effects of influenza virus infection according to underlying characteristics of the maternal-newborn population (e.g., nutritional factors, presence of maternal co-morbidities such as tuberculosis). Again, the importance of additional data from the two forthcoming BMGF-sponsored clinical trials was emphasized, as was the planned pooled analysis of data from the three BMGF trials [87].

6. Post-meeting addendum

Subsequent to this meeting, there have been several additions to the literature that warrant mention. In September 2016, the second BMGF-funded RCT of influenza immunization of pregnant women was published [92]. Between 2011 and 2014, 4193 women in Mali were randomized to receive trivalent inactivated influenza vaccine (experimental arm) or quadrivalent meningococcal conjugate vaccine (control arm). Vaccine efficacy for prevention of laboratory-confirmed maternal influenza between randomization and 6 months post-partum was 72% for influenza type A viruses and 73% for type B influenza. Overall, 9% of infants were born at a low birth weight (<2500 g); however, no differences in low birth weight or mean birth weight were observed between the vaccine groups overall, even when restricted to those infants born during the influenza season [92]. Evaluation of preterm birth was complicated by inconsistent assessment of gestational age in study participants. Among sub-groups of women with gestational age ascertained by first trimester ultrasound or last menstrual period, no differences were seen in risk of preterm birth by vaccine status.

Several observational studies of maternal influenza immunization have also been published since this meeting [93–100]. Generally, these new studies concur with earlier observational studies in finding no evidence of increased risk of preterm birth [93–95], SGA birth [93,94,96–98] or fetal death [95,97,99] associated with influenza immunization during pregnancy. However, one study, conducted in Laos, observed a significantly reduced risk of preterm birth associated with receipt of inactivated influenza vaccine during a time period of high viral circulation (adjusted RR: 0.69; 95% CI: 0.55–0.87) [98] and another from

Australia reported a large risk reduction for stillbirth (adjusted hazard ratio [HR]: 0.49; 95% CI: 0.29–0.84) [100].

7. Summary and conclusions

This consultation of experts was convened for the purpose of evaluating the literature concerning possible beneficial effects of maternal influenza immunization on birth outcomes. As noted in the summary of key points (Table 4), the opinion of meeting participants was that available published studies of influenza virus infection or vaccination during pregnancy have many limitations and fail to fully inform expectations regarding possible benefits of influenza vaccination on birth outcomes. This was particularly true for low-resource settings, where there were little-to-no burden of disease studies and few studies of influenza immunization during pregnancy. Moreover, participants agreed that the lack of evidence of harm is not equivalent to evidence of no harm. Given the paucity of information on first-trimester vaccine exposure and on long-term safety outcomes in children, it is more appropriate to conclude that maternal influenza immunization has no known adverse effects.

Despite the ability of RCTs to reduce confounding more fully than observational studies, the published and recently completed trials are small and restricted to pregnant women with low obstetrical risk, who were immunized during the 2nd or 3rd trimester. These characteristics limit their ability to evaluate the full range of birth outcomes, owing to insufficient power to study rare outcomes or detect small, but clinically meaningful, differences in common outcomes. In addition, randomization in mid-to-late pregnancy precludes assessment of outcomes relative to vaccination across a range of gestational ages, which is particularly important for early pregnancy outcomes such as miscarriage or congenital anomalies. Thus, observational studies of influenza immunization during pregnancy will likely continue to play a role in ongoing safety monitoring of vaccines, highlighting the importance of robust data sources, study designs and analytical approaches to mitigate methodological issues such as confounding bias.

Although maternal influenza virus infection is potentially an additional contributing factor to adverse pregnancy outcomes, with biologic plausibility supported by human data and animal models, it is unlikely to be a large contributor relative to other more common etiologies. The lack of consistent evidence that fetal health is adversely affected by maternal influenza virus infection [37] and a mounting body of evidence demonstrating issues with confounding bias in observational studies of influenza vaccination in elderly populations [79–82] justifies cautious interpretation of potential benefits of influenza vaccination for improving fetal outcomes [4]. Despite the conflicting evidence regarding potential beneficial effects of maternal influenza immunization on birth outcomes, strong evidence showing that influenza vaccination during pregnancy protects both mothers and newborn infants from influenza illness should continue to guide vaccine policy and investment strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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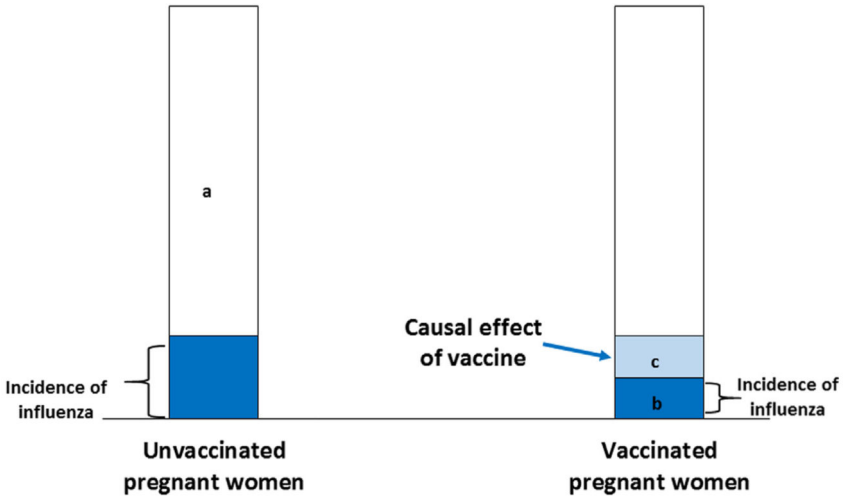

Fig. 1.

Counterfactual framework for causal effect of influenza vaccination. Adapted with permission from Hutcheon et al. [77]. [a]Even in the unvaccinated population, most pregnant women will not contract influenza virus infection. [b]Some women will contract influenza disease, irrespective of vaccination. [c]The causal effect of influenza vaccination is only realized among the small subset of women who would have gotten influenza if not vaccinated.

Table 1

Definitions and global prevalence estimates of preterm birth and stillbirth.

Outcome	Definition	Estimated global prevalence	Region with lowest and highest estimated prevalence	Ref.
Preterm birth	Live birth at less than 37 completed weeks of gestation	11.1 per 100 live births in 2010	Lowest: Eastern Asia (7.2%)[a] Highest: Southeastern Asia (13.6%) and Southern Asia (13.3%)	Blencowe et al. [12]
Stillbirth[b]	Spontaneous fetal death in mid-to-late gestation	18.4 per 1000 total births in 2015[c]	Lowest: Developed regions (3.4 per 1000 total births) Highest: Sub-Saharan Africa (28.7 per 1000 total births)	Lawn et al. [22]

[a] In developed regions, the estimated rate was 8.6% [12].

[b] Definitions of stillbirth vary between studies and countries. Although many countries in developed regions define stillbirth from an earlier gestational age (commonly from 22 completed weeks of gestation), the WHO recommends that stillbirth be defined as a fetal death at 28 weeks or later for international comparisons.

[c] Estimated global prevalence based on the WHO definition of 28 weeks of gestation or later.

Table 2

Study quality issues and evidence gaps identified in WHO-initiated systematic reviews of influenza virus infection during pregnancy.

Literature on risks of severe influenza outcomes among pregnant women [36]	
Quality issues in primary studies	• Evidence quality was low to very low (GRADE assessment) • Primary analysis in many studies compared pregnant women to non-pregnant women from a broad range of patient ages, not just to women of reproductive age • Inadequate control for potential confounding variables
Evidence gaps	• Limited evidence from seasonal epidemics • Limited evidence from low-resource settings • Unknown whether pregnant women with influenza are hospitalized due to disease severity or for precautionary reasons related to concerns for fetal wellbeing
Literature on risks of influenza virus infection during pregnancy to the fetus [47]	
Quality issues in primary studies	• Evidence quality was low to very low (GRADE assessment) • Most studies relied on non-laboratory confirmed measures of influenza disease, based on seeking medical care • High heterogeneity precluded meta-analysis for most birth outcomes • Highly inconsistent definitions of stillbirth • Inadequate control for potential confounding variables
Evidence gaps	• Limited evidence from seasonal epidemics • Limited evidence from low-resource settings • Small number of comparative studies addressing influenza disease and pregnancy outcomes, particularly for fetal death • Limited evidence on impact of maternal malnutrition or other contextual factors (e.g., co-infection with HIV or tuberculosis) • Lack of information on timing of influenza virus infection during pregnancy • No distinction between spontaneous and medically-initiated preterm birth

Table 3

Summary of results for birth outcomes from randomized controlled trials (RCTs) of influenza immunization during pregnancy.[a]

	Bangladesh RCT[b]			South Africa RCT[c]		
	Pneumococcal polysaccharide vaccine	**Influenza vaccine**	**p-value**	**Placebo**	**Influenza vaccine**	**p-value**
Overall comparison						
No. women randomized	168	172		1054	1062	
Proportion of preterm births (<37 weeks)						
n	14	10	p = 0.4	96	108	p = 0.4 [d]
%	8.4%	6.5%		9.4%	10.5%	
Mean birth weight	3027 g	3117 g	p = 0.09	3075 g	3035 g	p = 0.08
Proportion of infants with low birth weight (<2500 g)						
n	13	7	p = 0.2	122	133	p = 0.5 [d]
%	7.8%	4.1%		12.0%	13.0%	
Small-for-gestational age birth						
n	63	45	p = 0.05	NR	NR	
%	38.0%	28.0%				
Comparison among births during influenza season						
No. women analyzed	58	58		NR	NR	
Proportion of preterm births (<37 weeks)						
n	4	2	p = 0.4	NR	NR	
%	6.9%	3.5%				
Mean birth weight	2978 g	3178 g	p = 0.02	3089 g	3047 g	p = 0.07
Proportion of infants with low birth weight (<2500 g)						
n	5	1	p = 0.09	-	-	p = 0.2
%	8.6%	1.7%		9.8%	11.6%	
Small-for-gestational age birth						
n	26	15	p = 0.03	NR	NR	
%	44.8%	25.9%				

NR: not reported.

[a] In September 2015, when this meeting took place, there were two published RCTs of influenza immunization during pregnancy available for review [2,3].

[b] Results compiled from publications by Zaman et al. [2] and Steinhoff et al. [88].

[c] Results compiled from publication by Madhi et al. [3] and conference abstract by Simões et al. [89].

[d] Calculated from raw data provided.

Table 4

Summary of key points across all discussions.

Influenza burden of disease on the fetus
• Since maternal influenza disease is central in the proposed biological mechanism by which influenza vaccination could improve pregnancy outcomes, estimates of the magnitude of risk among women who develop influenza infection are needed to interpret the full impact of maternal influenza immunization on birth outcomes
• Adverse pregnancy outcomes are complex conditions with multiple, often overlapping, etiologies. Given the number of factors that could theoretically influence each birth outcome, any one of them will likely have a small impact independent of the others
• For example, even in rural low- and middle-income countries where the burden of SGA birth is high, influenza would not be expected to cause a large fraction of SGA birth
Maternal influenza immunization and birth outcomes
• Observational studies and RCTs of influenza vaccination during pregnancy provide mixed evidence suggesting reduced risk of adverse birth outcomes
• The degree to which selective uptake of influenza vaccine could create a “healthy vaccinee” bias in the obstetric population is unclear, but large, significant risk reductions reported by some observational vaccination studies may implicate issues that have been well described in vaccine studies in the elderly
• Taken together, confounding biases and other methodological limitations are compelling explanations for the protective effects reported in some observational studies of influenza vaccination in pregnancy
• Given that observational studies are likely to continue to play a role in influenza vaccine safety monitoring during pregnancy, appropriate data sources and methodologies to support those activities are required. Presently, limited availability of data on fetal death and the paucity of registries with detailed influenza vaccine administration documentation to pregnant women (such as date of vaccination) pose challenges for ongoing safety evaluation
Additional outstanding evidence gaps
• Long-term safety data, particularly among children exposed to influenza vaccination in utero
• Impact of different vaccine components and adjuvants
• Methodologies are required to detect potential “healthy vaccinee” bias in observational studies of influenza vaccination during pregnancy
• The impact of gestational timing of exposure to either influenza virus infection or influenza vaccination
• The safety of first-trimester influenza vaccination is an important area for future studies, given the critical time window for fetal development and the recommendation that women be immunized against influenza in any trimester of pregnancy