Interim Report to WHO Initiative for Vaccine Research

WHO TASKFORCE TO EVALUATE INFLUENZA DATA TO INFORM VACCINE IMPACT AND ECONOMIC MODELLING

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Executive Summary

As part of the WHO maternal influenza immunization agenda, the WHO Initiative for Vaccine Research (IVR) convened a Taskforce during 2014 to advise in the review of key variables for influenza vaccine impact and health economic modelling studies. The Taskforce is a working group of the WHO Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC) and functions as one of the sub-groups of the WHO Vaccine Preventable Disease (VPD) Burden and Impact Assessment Framework.

The Taskforce has three Workstreams; each is led by a different team reviewing influenza disease risk and morbidity in pregnant women, children <6 months of age, and the fetus, as well as vaccine performance to reduce influenza disease in these groups. Supporting data have been sought from a review on vaccine performance being conducted by the Aga Khan University and from clinical trials of influenza vaccine during pregnancy conducted in South Africa, Nepal, and Mali; however, data from the latter two of the clinical trials are not included in this report. Within the three Workstreams, the Taskforce has four objectives: 1) to determine key parameters needed for influenza vaccine impact and health economic modelling studies, with a focus on pregnant women and low-resource settings; 2) to determine evidence-based assumptions for these key parameters; 3) to evaluate the quality of existing data; and 4) to provide recommendations to WHO for addressing data gaps. The Taskforce will focus primarily on burden measures such as incidence (or attack rate) for influenza virus infection, symptomatic disease, hospitalization, and mortality; within the Fetal Effects Workstream, burden measures include risk (cumulative incidence rates) of preterm or small-for-gestational age birth and fetal loss, along with relative differences in these measures comparing women with and without influenza illness. For each Workstream, the lead investigator is conducting a systematic literature review and findings have been presented to a large group of experts – the members of the broader Taskforce – to obtain feedback on methodology, analysis, and interpretation.

For the review of burden among pregnant women, no results are available currently. A secondary analysis evaluated risk of severe influenza among pregnant women. Based on meta-analysis of 148 comparative observational studies of people with influenza virus infection comparing pregnant women to either all other persons or less frequently all other women of child-bearing age, pregnancy was associated with hospitalization (odds ratio [OR], 2.9; 95% CI, 1.6 to 5.5) but not mortality (OR, 1.0; 95% CI 0.81 to 1.3), pneumonia (OR, 1.8; 95% CI, 0.72 to 4.5), receipt of mechanical ventilatory support (OR, 1.2; 95% CI, 0.70 to 2.1), or ICU admission (OR, 0.89; 95% CI, 0.65 to 1.2). All outcomes except hospitalization were considered to have a low quality of evidence.

Among children <6 months of age, 22 studies provided data, including 14 studies from a previously published review. A meta-analysis of the 14 original studies found a pooled incidence of severe or hospitalized influenza of 3.1 per 1000 child-years (95% CI, 2.3 to 4.2). While most studies had incidences between 1 and 10 per 1000 child-years, the range extended from 0.62 to 17 per 1000 child-years when including more recent studies. A second review of influenza disease burden in this age group is ongoing. Preliminary findings include limitations in the number of high quality studies.

For evaluation of fetal effects comparing pregnant women with and without influenza illness, 20 comparative observational studies were included that compared one or more relevant Taskforce
outcome among pregnant women with influenza virus infection (defined clinically or microbiologically) to pregnant women without influenza virus infection. Ten studies originated from the United States and the remainder from Canada or Europe, and studies used various methods to assign influenza status. Among six high-quality studies reporting data on preterm birth (gestational age <37 weeks), baseline preterm birth rates among uninfected women varied from 5.4% to 12% while rates among influenza-infected women varied from 7.2% to 24%. Three of these studies reported data for severe illness due to pandemic 2009 H1N1 with adjusted odds ratios of 1.3 to 4.0, with two studies reaching statistical significance. Influenza did not increase risk of preterm birth in two studies of pandemic 2009 H1N1 that evaluated a range of maternal illness severity, nor in two studies from non-pandemic seasons (one study each on severe and mixed severity seasonal influenza). Among four studies reporting low birth weight (<2,500 grams) that adjusted for gestational age, there were no significant differences between exposure groups (range in odds ratios, 1.1 to 1.3). Two high-quality studies provided data on fetal loss, both involving pandemic 2009 H1N1 with one finding a risk ratio of 4.2 (95% CI, 1.4 to 12) and one 1.9 (95% CI, 1.1 to 3.4).

For the evaluation of vaccine efficacy in pregnant women and their children <6 months of age, the Taskforce is taking advantage of two systematic reviews of influenza vaccine performance in pregnancy. The Taskforce will meta-analyse the highest quality evidence from these reviews to estimate vaccine efficacy as outlined in the activity objectives. Review of the literature has identified only one randomized clinical trial with pre-specified laboratory-confirmed influenza disease endpoints. In the identified randomized clinical trial, 2116 pregnant women without HIV and 194 pregnant women with HIV were enrolled in Soweto, South Africa. The primary clinical endpoint was mild, acute respiratory illness with laboratory confirmation of influenza virus infection. Vaccine efficacy was identified for this outcome for HIV-infected and uninfected women and HIV-uninfected children age <6 months. There were no reported differences in terms of vaccine impact on severe influenza disease in mothers or children <6 months of age. Among newborns (both exposed and unexposed to HIV), there was no statistical difference between vaccine groups for low birth weight, median birth weight, miscarriage (fetal death <28 weeks), or stillbirth (fetal death ≥28 weeks).

Evaluations are continuing, and results will be updated in the future for all Taskforce activities. Based on the existing data, several conclusions can be reached.

- **Interpretation and comparison**: Few data exist on the burden of influenza-associated outcomes following infection during pregnancy to the pregnant woman, fetus, or newborn. Many studies that have been conducted have methodological issues that make interpretation difficult. Comparison across studies is difficult due to differences in case definitions (including methods for ascertaining influenza), period of assessment during pregnancy, and potentially different effects of pandemic 2009 H1N1 compared to other influenza strains or years.

- **Influenza risk and burden in pregnant women**: In predominantly high-income settings, influenza increases the risk of hospitalization, but not of severe disease, among pregnant women.

- **Influenza risk and burden in children <6 months of age**: There are limited published data on influenza disease risk and burden in children <6 months of age. Many of these studies are small or have methodological issues, which limit their utility in estimating the burden of severe influenza disease in this group.
• **Influenza risk to developing fetus:** There are limited published data from comparative studies on the risk of maternal influenza disease on birth outcomes, and they have methodological differences and limitations, which make interpretation a challenge. There is some replicated evidence from higher-quality studies suggesting that severe pandemic 2009 H1N1 disease – but not mixed severity disease or disease due to seasonal influenza – during pregnancy was associated with preterm birth. Studies of mild or subclinical maternal influenza disease did not show an association with preterm birth during the 2009 pandemic or during non-pandemic seasons.

• **Vaccine efficacy to prevent influenza disease:** There are limited high quality published data from randomized clinical trials; however additional clinical trial data are expected soon. Evidence from one large adequate quality trial on the effectiveness of inactivated influenza vaccine during pregnancy suggests reduced laboratory-confirmed influenza among women and their babies, but no evidence was found of impact on severe influenza disease or on newborn outcomes. More well-designed, large scale randomised controlled trials are needed with appropriate controls to establish the benefit of maternal influenza vaccination during pregnancy.

Taken as a whole, influenza disease burden data may not be sufficient to inform decision-making in many countries regarding routine immunization of pregnant women with influenza vaccine. This situation is particularly true for low-resource settings, where results may differ substantially due to differences in influenza epidemiology, background prevalence of underlying diseases, severity of disease on presentation, likelihood of secondary bacterial infection, and background prevalence of adverse fetal outcomes. Without baseline disease burden estimates, including vaccine preventable disease incidence against severe clinical outcomes such as pneumonia or respiratory disease deaths, the public health utility of incorporating influenza vaccine into national immunization programs remains unknown.
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1. Background
In 2012, the World Health Organization (WHO) released a position paper on influenza vaccination stating that pregnant women should have the highest priority for seasonal influenza vaccination in countries considering the initiation or expansion of influenza immunization programs. Despite the WHO recommendation, maternal influenza immunization has not been incorporated into routine immunization programs in many low-resource settings. In 2013, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) requested that WHO develop a process and a plan to move the maternal immunization agenda forward in support of an increased alignment of data safety evidence, public health needs, and regulatory processes.

To date, the evidence on the impact and cost of vaccines of maternal immunization programs remains limited. As part of the WHO maternal influenza immunization agenda, the WHO Initiative for Vaccine Research (IVR) convened a Taskforce in December 2014 to provide guidance to technical reviews of key variables for influenza vaccine impact and health economic modelling studies.

The Taskforce is a working group of the WHO Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC) and functions as one of the sub-groups of the WHO Vaccine Preventable Disease (VPD) Burden and Impact Assessment Framework. The Taskforce was asked to inform efforts by IVR to promote evidence-based implementation research for influenza vaccine programs.

The Taskforce will function as one of the sub-groups of the WHO Vaccine Preventable Diseases Burden (VPD) and Impact Assessment Framework. In line with recommendations made by IVIR-AC in 2014, a virtual information hub on the burden of vaccine preventable disease and impact assessment was created with the following aims:

1. To provide transparent information to principal users on VPD burden and impact assessment work such as National Immunization Technical Advisory Groups (NITAGs), decision makers and others
2. To identify gaps and priorities of research for researchers, policy makers and donors
3. To bring issues to attention to other ACs and independent review groups as appropriate

The virtual hub will benefit and utilize expertise from existing WHO advisory groups (e.g. Immunization Practices Advisory Committee, Product Development for Vaccines Advisory Committee) and other independent review groups, and it will provide services to donors and policy making bodies.

The Taskforce objectives are the following: 1) To determine key parameters needed for influenza vaccine impact and health economic modelling studies, with a focus on immunization in low-resource settings and pregnant women; 2) To determine evidence-based estimates for these key parameters; 3) To evaluate the quality of existing data informing these estimates; 4) To recommend future research to address existing data gaps. Taskforce participants include a multidisciplinary group of experts with extensive experience in disease modelling, health economics, influenza epidemiology, and perinatal epidemiology. The Taskforce includes a Chair (Bradford Gessner) and

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1 For IVIR-AC recommendations 2014 see: http://www.who.int/wer/2015/wer9001_02.pdf?ua=1
For IVIR-AC full report 2014 see: http://www.who.int/immunization/research/committees/IVIRAC_meeting_report_WHO_IVB_15_01_eng.pdf?ua=1
three Workstream Leads (Niranjan Bhat, Deshayne Fell, Mark Loeb), and is supported by WHO and its consultants. Two IVIR-AC members participate on the Taskforce, to ensure alignment between the groups. WHO Initiative for Vaccine Research and its consultants serve as the secretariat for the Taskforce.

To support the Taskforce efforts, WHO commissioned reviews on the following topics:

- Influenza disease risk and burden in pregnant women
- Influenza disease risk and burden in children < 6 months of age (in partnership with PATH)
- Adverse fetal outcomes associated with maternal influenza illness and infection
- Effect of interventions during pregnancy on birth weight and prematurity
- Influenza vaccine efficacy/effectiveness in pregnant women and newborn children
- Methodological issues regarding observational studies of the effect of influenza vaccination on pregnancy outcomes (in partnership with PATH)

In addition, the Taskforce has taken advantage of recent systematic reviews published on maternal influenza immunization performance and safety to informs its deliberations.

This interim report describes the progress of the Workstreams, including preliminary data available from the commissioned reviews. The report was written by the Taskforce Chair, Workstream Leads, and Taskforce Rapporteur and the interpretation of the data is their own. A final consensus report by the overall Taskforce is anticipated during the third quarter 2015.

2. Incidence of Severe Influenza among Pregnant Women

Objectives of activity

This study is in progress. Objectives include to determine evidence-based estimates for the following parameters:

- Influenza attack rate among pregnant women (infection)
- Influenza attack rate among pregnant women (symptomatic)
- Influenza-associated hospitalization incidence rate among pregnant women
- Influenza-associated mortality incidence rate among pregnant women
- Influenza disability adjusted life years lost among pregnant women

Although the population of interest is pregnant women in low-resource settings, we are including studies from any site, trying to be comprehensive with the understanding that human resources and time are limited.

Procedures

We are conducting a systematic literature review using MEDLINE, EMBASE, CINAHL, and the Cochrane Library. A broad search strategy based on relevant medical subject headings and keywords was developed in MEDLINE by a medical librarian. Additionally we will reach out to experts in the field to ensure that we have not missed relevant published data. See Appendix 1: Flow diagram showing study selection process.
Progress

We have completed the search and the initial abstract review. We are in the process of conducting the manuscript review.

Interim results

In the initial literature search we identified 1,043 abstracts after deduplication. We reviewed those abstracts and identified 30 abstracts that were potentially relevant. We are currently in the process of collecting full text articles for further review.

Interpretation of results

Not available at this stage of review.

3. Risk of Severe Influenza among Pregnant Women

Objectives of activity

To quantify the effect of pregnancy on the progression from influenza virus infection to severe disease and to summarize the evidence for pregnancy as a risk for severe influenza disease

Planned procedures

Systematic review and meta-analysis of observational studies including cohort, case-control, cross-sectional, and ecological studies that reported on pregnancy as a risk factor for severe outcomes from influenza virus infection was conducted. A search of MEDLINE, EMBASE, CINAHL, and CENTRAL to identify studies reporting on outcomes of interest in pregnant women with evidence of influenza virus infection in comparison to non-pregnant patients was done. Outcomes included community-acquired pneumonia, hospital admission, admission to intensive care units (ICU), receipt of mechanical ventilatory support, death, and a combined outcome of ICU admission or death. A random effects model was used to obtain risk estimates. Ecological studies were summarized descriptively. See Appendix 2: Flow diagram showing study selection process.

Progress

The systematic review and meta-analysis have been completed.

Interim results

A total of 148 non-ecological and 10 ecological studies of pregnant women with evidence of influenza virus infection were included. There was a higher risk for influenza-associated hospital admission in pregnant versus non-pregnant patients (of all ages and both sexes) in meta-analysis (n=14; odds ratio [OR] 2.94, 95% confidence interval 1.58-5.47). With women of reproductive age (WRA) as the comparator, the association remained (n=2; OR 3.3, 0.52-20) as it did an analysis limited to low- and middle-income countries (LMIC) (n=3; OR 2.1, 0.49-9.0). Meta-analysis found no association between pregnancy and mortality overall (n=92; OR 1.03, 0.81-1.3) or with WRA as the comparator (n=17; OR 0.94, 0.52 to 1.7) but did identify an association from LMICs (n=36; OR 1.6,
1.1-2.2). There was no association between pregnancy and pneumonia overall (n=9; OR 1.80, 0.72-4.49) or with WRA as the comparator (n=3; OR 1.1, 0.29-4.1). There was no association between pregnancy and mechanical ventilator support overall (n=26; OR 1.21, 0.70-2.08) or with WRA as the comparator (n=5; OR 0.88, 0.62-1.3). There was no association between pregnancy and ICU admission overall (n=45; OR 0.89, 0.65-1.2) but a strong association existed with WRA as the comparator (n=10; OR 0.51, 0.42-0.62).

In ecological studies, 4 of 8 studies reported higher mortality rates, 4 of 4 studies found higher hospital admission rates, and 2 of 2 studies found a higher ICU admission rate among pregnant women. In individual level studies, the average points in the risk of bias assessment using the Newcastle-Ottawa Scale was 6 out of a maximum of 9 points (interquartile range 6-7, range 3-8). Applying the GRADE framework, we downgraded the quality of evidence for all outcomes for either high heterogeneity in the meta-analysis or inconsistencies when comparing the finding in individual-level studies to ecological studies. Given the large confidence intervals around the summary estimate that could not rule out patient-important differences, all outcomes other than hospital admission were downgraded further. Hospital admission was upgraded based on the large effect observed. Therefore, all outcomes other than hospital admission were deemed to be based on low quality of evidence, while the increased risk of hospital admission was based on low-level evidence.

**Interpretation of results**

Meta-analysis of non-ecological studies demonstrated a higher risk of influenza-associated hospital admission for pregnant women, but no increase in other severe influenza events. When comparing pregnant women to non-pregnant women of childbearing age, pregnant women were at less risk of ICU admission. In contrast, some ecological studies suggested a higher risk of death and ICU admission. Given the limitations of ecological study designs, influenza virus infection in pregnancy may not be associated with severe outcomes but rather of a higher risk of hospitalization given the same level of disease severity. While the prevention of influenza hospitalization among pregnant women may justify targeting them for immunization, we recommend further research to determine whether pregnant women with influenza are hospitalized due to severity of disease or for precautionary reasons.

**4. Risk of Severe Influenza among Children <6 Months**

**Objectives of activity**

The objectives of this review were to summarize rates of pneumonia, hospitalization, and death among infants <6 months infected with seasonal or pandemic influenza virus.

**Planned procedures**

The Taskforce will take advantage of two systematic reviews of influenza disease burden in children. The first is a re-analysis of a previously published systematic review of influenza disease in children <5 years by Nair et al.\(^2\) In that review, a search of Medline (Ovid), Embase, CINAHL, Global Health,

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Web of Science, WHOLIS, LILACS, IndMed, grey literature (SIGLE), and Chinese language databases was conducted by H. Nair, et al., supplemented by a hand search of the literature, capturing studies published between Jan 1, 1995, and Oct 31, 2010, that described incidence rates for influenza disease among children less than five years of age. In addition, a comprehensive set of investigators worldwide was contacted by that group to obtain unpublished influenza incidence data. For the purposes of this Taskforce, data on influenza incidence in children <6 months of age were extracted from the full set. Subsequently, an updated query was conducted, searching only Ovid/Medline and Embase, and restricted to English language publications only, and focusing on studies reporting data on children <6 months of age. For these two databases, the same search queries and eligibility criteria as used in the original search were employed, updated to capture studies published during 2010-2014. No unpublished data were pursued or included. See Appendix 3: Flow diagram showing study selection process.

As an adjunct to this review, the Taskforce also will re-analyse data from a previous study on influenza disease risk by D. Mertz et al.³ This study included all observational comparative studies of severe influenza virus infection to quantify the risk associated with multiple different underlying factors (age, pregnancy, chronic disease). The original literature search of MEDLINE, EMBASE, GLOBAL HEALTH, CINAHL, and CENTRAL was conducted to identify studies (up to March 2011). In the re-analysis, the original systematic review database was searched to identify studies reporting on outcomes of interest in children <6 months of age with evidence of influenza virus infection was done. Outcomes included community-acquired pneumonia, hospital admission, death, and DALYs lost. See Appendix 4: Flow diagram showing study selection process.

Progress

For the re-analysis of Nair et al, the <6 months subset from the original analysis has been extracted. The updated literature search has been conducted, including full-text review. Incidence rates from these two sets have been summarized concurrently.

For the re-analysis of Mertz et al, the anticipated completion date is June 16, 2015 (for children of all ages).

Interim results

Re-analysis of Nair et al.

Of the 43 studies included in the original systematic review (27 published, 16 unpublished), 14 included data on influenza incidence among children <6 months of age. The updated search yielded 8 published studies that met these same eligibility criteria.

Of the outcomes under consideration, only severe or hospitalized acute respiratory infection with confirmed influenza and all cause severe or hospitalized acute lower respiratory illness (ALRI) were identified. Other outcomes, including influenza virus infection (all severities), influenza-associated mortality, and influenza-associated disability-adjusted life-years (DALYs) lost, were not reported in the eligible studies.

Most of the 22 studies reported incidences of severe or hospitalized ARI with confirmed influenza between 1 and 10 per 1000 child-years. Rates reported in the updated search were more heterogeneous (range 0.62-18 per 1000 child-years).

A preliminary meta-analysis of the 14 studies extracted from the original systematic review produced a pooled estimate of 3.1 (95%CI 2.3, 4.2) per 1000 child-years using a random effects model, and 2.2 (95%CI 2.1, 2.3) per 1000 child-years using a mixed effects model. I-squared statistic was 96.1% (p=0.000), indicating considerable heterogeneity.

Next steps include plans to contact authors of some of the more recently identified studies, to clarify data or methods. Investigators who have recently reported on broader age groups may be approached to consider re-analysis of children <6 months of age. However, we acknowledge that calculating an appropriate denominator may require more in-depth demographic methods.

Results from the two searches will be combined to produce an updated meta-estimate and forest plot. Further refinement of these results will include exclusion of 2009 pandemic data, as well as sensitivity analyses, sub-analyses, and descriptive analyses based on the following characteristics: tropical vs. temperate climate, high income vs. low or low and middle income countries; by year; by method of laboratory confirmation; passive vs. active ascertainment; and population size.

Methods for quality assessment continue to be developed, but will include a qualitative examination of characteristics such as study population size, method and completeness of case ascertainment, completeness of specimen collection, method of laboratory testing, and adjustment for bias.

We will conduct a formal systematic query covering data from 2010 onward, based on the strategies of the original review. Additional studies identified through this more rigorous search will be incorporated into the analyses described above.

Re-analysis of Mertz et al.

A total of 62,839 citations were identified with 47,874 records after duplicates were removed, among which 13 studies were found to report the outcomes of interest. This included screening citations from a previous systematic review from which the 13 were identified as well as screening 31,811 citations of which none reported outcomes of interest among the target age group. Eight studies of seasonal and five of pandemic H1N1 influenza were included.

The re-analysis estimated that of children with seasonal influenza virus infection, pneumonia occurred among 20% (183/900), hospitalization among 40% (313/776), and mortality among 0.4% (5/1160). The average New Castle-Ottawa scores were 6.0, 6.5, and 6.0 respectively.

Of children with pandemic influenza, pneumonia occurred among 64% (7/11) and mortality among 14% (5/35). The average New Castle-Ottawa scores were 5.5 and 5.8 for pneumonia and death respectively.

Additional data review
Members of the Taskforce also reviewed studies examining the proportion of specific outcomes testing positive for influenza. However, this evaluation does not provide a measure of disease burden.

**Interpretation of results**

**Re-analysis of Nair et al.**

Data regarding the burden of influenza in young infants are limited, both in terms of quantity as well as breadth of outcomes reported. Although the range of incidence rates for severe influenza in infants is relatively small (1-10/1000 child-years), earlier studies demonstrated considerable heterogeneity. We will examine major factors contributing to this heterogeneity and to heterogeneity in later studies. Population-based incidence rates of laboratory-confirmed illness may provide the most consistent method of comparing data across sites, however several limitations exist, including small case counts, low rates of testing in this age group, poor sensitivity for some potentially attributable events (e.g. secondary bacterial illnesses), inability to assign causality between influenza virus infection and outcomes or to rule out causality when influenza is not identified, variations in methods for sample collection, and different laboratory tools.

Future research will need to include additional prospective cohort and surveillance studies to increase the quantity and breadth of data. These studies should also evaluate primary drivers of heterogeneity. Influenza vaccine probe studies that measure the vaccine-preventable incidence and influenza-attributable fraction of clinical disease syndromes may be more informative in estimating the complete burden of disease in a population, as they avoid the concerns regarding establishing causality. For the 0-5 age group, such a study would rely on indirect protection, since vaccines are not currently approved for use in children age <6 months. For example, in a community randomized trial, all age groups in the intervention group with an online indication would receive vaccine and the preventable incidence would be estimated as the difference in incidences between the children <6 months of age in control communities and those in intervention communities. Since many of the same issues (including paucity of data) exist for children age 6-23 months, the evaluation of children age <6 months could be done as a sub-analysis of a study whose primary goal is to assess burden in these older children. Ecologic studies modelling influenza-attributable deaths also may need to be considered but as shown in the data on pregnancy associated outcomes; such studies may further cloud the picture when results disagree with other study designs.

**Re-analysis of Mertz et al.**

To date, our results show that there are few studies that have evaluated influenza outcomes (pneumonia, hospitalization, death, DALYs lost) among children <6 months of age. Many of the studies are small, retrospective, and do not begin with a community-based inception cohort. Studies based on hospital cohorts cannot be extrapolated to the entire community since the former represent a sub-set of severe influenza.

**5. Adverse Fetal Outcomes Associated with Maternal Influenza**

**Objectives of this activity**
The primary objective was to assess the association between maternal influenza illness during pregnancy on the risk of adverse fetal outcomes, as compared with no maternal influenza illness during pregnancy through a systematic literature review. Secondary objectives were to provide estimates for the WHO Taskforce key parameters, to identify key limitations in the existing evidence, and to make recommendations for future research.

**Planned procedures**

We conducted an electronic literature search of indexed studies in MEDLINE, EMBASE, CINAHL, and Cochrane from inception to Dec 5, 2014. A broad search strategy based on relevant medical subject headings and keywords was developed in MEDLINE by a medical librarian. Screening was carried out by two independent reviewers to identify studies: 1) using comparative observational designs (i.e., cohort, case-control, cross-sectional); 2) examining influenza illness/infection during pregnancy compared with no influenza illness/infection during pregnancy; and 3) addressing any of the following outcomes: preterm birth, small for gestational age, pregnancy loss (i.e., miscarriage or stillbirth), or influenza disability adjusted life years lost. See Appendix 5: Flow diagram showing study selection process.

**Progress**

We have completed the literature search and screening process, extracted detailed information from all included studies, and summarized the data for each review outcome. Data synthesis, critical appraisal, and formal assessments of the quality of the evidence are ongoing. The anticipated completion date is June 2015.

**Interim results**

Electronic literature searches identified 1,923 titles and abstracts. We reviewed the full text of 98 articles and included 20 comparative observational studies reporting one or more review outcomes. Studies originated from 6 countries, with 10 performed in the United States, two originating from Canada and the remainder from European countries. Several different approaches were used to classify pregnant women as “exposed” or “unexposed”. In general, most studies based exposure classification on influenza illness (with or without lab-confirmation), with substantial heterogeneity in the methods used to define the exposed and comparison groups.

There was high clinical heterogeneity across the 15 studies assessing preterm birth. Across all study populations, the baseline risk of preterm birth ranged from 5.2% to 12% in the unexposed groups and from 4.0% to 26% in the exposed groups. In general, studies that used an exposure definition based on more severe maternal illness (either because all or most exposed subjects were hospitalized, or due to selective lab-testing carried out only on women with clinical symptoms of severe influenza illness) reported a preterm birth risk in excess of 12 per 100 live births among women with influenza illness. Statistical heterogeneity across the 15 studies was also high ($I^2$=97%, 95% CI: 97–98). Subgroups created to assess results across studies with greater similarity in methods of exposure measurement, quality, and influenza season characteristics were limited to a small number of studies. Among three H1N1 pandemic studies with exposure based on severe maternal influenza illness, the adjusted odds ratios comparing exposed with influenza-negative women ranged from 1.3 to 4.0, with 95% confidence intervals that excluded the null value in two of the
three studies. Among two H1N1 pandemic studies with exposure defined as any influenza illness regardless of severity, there was no elevated risk of preterm birth. There was also no association between preterm birth and influenza illness in the two highest quality studies from seasonal epidemic years, whether the exposure definition was based on hospitalization for influenza or represented a range of maternal influenza illness severity.

Other review outcomes were reported by a smaller number of studies, and data synthesis and interpretation is ongoing. Briefly, the studies that assessed small for gestational age yielded inconsistent results: three of the studies reported no significant difference between the exposure groups, with ratio effect estimates ranging from 0.71 to 0.98, while three other studies reported a significantly increased risk of small for gestational age in exposed women, with ratio effect estimates ranging from 1.6 to 2.4. Confidence intervals were overlapping between the group of studies showing no effect and those showing significantly elevated risk of small for gestational age. Among nine studies that assessed fetal death, six failed to provide a formal definition for the outcome and six were constrained by very low numbers of events. Among the two highest quality studies, both of which were conducted during the 2009–2010 H1N1 pandemic, maternal H1N1 illness was associated with a significantly increased risk of fetal death. The magnitude of the two ratio estimates varied, likely due to different exposure definitions and ascertainment of fetal death from different gestational age thresholds (Norway: hazards ratio = 1.9, 95% CI: 1.1–3.4; United Kingdom: odds ratio = 4.2, 95% CI: 1.4–12).

Although formal quality assessments are not complete, several key limitations in the evidence have been identified. In addition to the usual limitations of observational study designs, a particular concern in several of the studies is the potential for diagnostic ascertainment bias (specifically, differential assessment and ascertainment of influenza among women with complicated pregnancies, compared with women having uncomplicated pregnancies). To augment our other quality assessments, we are currently evaluating all studies for differential diagnostic ascertainment and will incorporate these findings into our final interpretation of results. Other identified limitations include the lack of evidence on timing of influenza exposure during gestation, the lack of evidence on spontaneous preterm birth (which may have a different association with influenza virus infection than iatrogenic preterm birth), and a lack of evidence from comparative studies in resource-constrained settings, where the impact of maternal influenza on fetal outcomes may differ in part due to different underlying baseline risk of adverse outcomes, or due to lower rates of influenza vaccination in the obstetrical population.

**Interpretation of results**

Among the studies included in this review, there are notable deficits in methodologies and particularly high heterogeneity in exposure measurement, resulting in inconsistency across studies. The evidence suggests an association between pandemic H1N1 influenza illness during pregnancy and preterm birth and fetal death, particularly from studies using an exposure definition based on severe maternal influenza illness. Since there is concern that some studies may be affected by diagnostic ascertainment bias, the true magnitude of the impact of maternal influenza illness during pregnancy remains unclear and is the subject of ongoing critical assessment. Specific recommendations for future research are yet to be deliberated by this Workstream.
6. Vaccine Efficacy to Prevent Influenza Disease

Objectives of this activity

The primary objectives of this activity are to estimate the efficacy of influenza vaccination during pregnancy to prevent severe influenza disease among pregnant women and their children <6 months of age, and to estimate the efficacy of influenza vaccination during pregnancy to prevent important adverse birth outcomes including small for gestational age, preterm birth, and low birth weight.

Planned procedures

The Taskforce will take advantage of two systematic reviews of influenza vaccine performance in pregnancy.

The Taskforce will meta-analyse the highest quality evidence from these reviews to estimate vaccine efficacy as outlined in the activity objectives.

A systematic search was conducted in the Cochrane Pregnancy and Childbirth Group's Trials Register through January 2015 for all randomised controlled clinical trials (including cluster-randomised trials) and quasi-randomised trials evaluating viral influenza vaccination during pregnancy compared with no vaccination or placebo.

Progress

Review of the literature has identified only one randomized clinical trial with pre-specified laboratory-confirmed influenza disease endpoints. The Taskforce is aware of two additional randomized clinical trials that are underway and that have not yet been published, and the Taskforce has requested data from these trials to include in its review.

Interim results

In the identified randomized clinical trial, 2116 pregnant women without HIV and 194 pregnant women with HIV were enrolled in Soweto, South Africa. The primary clinical endpoint was mild, acute respiratory illness with laboratory confirmation of influenza virus infection. Among HIV-uninfected women and their children <6 months of age, vaccine efficacy to prevent influenza virus infection was 50.4% (14.5 to 71.2) and 48.8% (11.6 to 70.4). Among HIV-infected women, the vaccine efficacy to prevent influenza virus infection was 57.7% (0.2 to 82.1). There were too few influenza outcomes among newborns born to women with HIV for calculation of vaccine efficacy in this group. There were no reported differences in terms of vaccine impact on severe influenza disease in mothers or children <6 months. Among newborns (both exposed and unexposed to HIV), there was no statistical difference between vaccine groups for low birth weight, median birth weight, miscarriage (fetal death <28 weeks), or stillbirth (fetal death ≥28 weeks).

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Interpretation of results

There are limited clinical trial data informing Taskforce review of vaccine efficacy to prevent influenza disease, although two additional trials are ongoing and will provide further quality evidence. In the only high quality trial, influenza vaccine prevented about half of the influenza virus infections in pregnant women without HIV and their newborn children. Vaccine efficacy was higher in pregnant women with HIV, with no data regarding vaccine efficacy in children with in-utero exposure to HIV. The trial endpoints were mild acute influenza disease, and there are no clinical trial data on the efficacy of maternal influenza immunization to prevent severe influenza disease in pregnant women or their children. Influenza vaccine was not associated with any benefit compared to placebo to prevent adverse birth outcomes.
Appendix 1: Flow Diagram for Pregnancy Burden Systematic Review

Records identified through initial search:
EMBASE   n = 816
MEDLINE  n = 569
CINAHL   n = 112
COCHRANE n = 46
TOTAL    n = 1,543

# of records after duplicates removed n = 1043

# of studies meeting eligibility criteria for influenza burden in pregnant women after abstract screening n = 30

# of studies meeting eligibility criteria for influenza burden in pregnant women after manuscript screening (IN PROCESS)
Appendix 2: Flow Diagram for Pregnancy Risk Systematic Review

Records identified through database searching:
- EMBASE  n = 13,408
- MEDLINE  n = 10,013
- GLOBAL HEALTH  n = 4,962
- CINAHL  n = 1,586
- CENTRAL  n = 67
- TOTAL  n = 62,839

Additional records identified through other sources
From bibliographies of relevant studies and review articles  

# of records after duplicates removed n = 19,980
# of records after duplicates with original search removed n = 17,013

# of records meeting eligibility criteria for full text screening; n = 950

# of records excluded based on screening of titles and abstracts; n = 16,063

Studies excluded in full-text screening/data collection:
- No original data provided  n = 39
- No comparison of interest reported  n = 668
- Not meeting diagnostic criteria  n = 3
- Other reasons for exclusion  n = 4
- Language other than English  n = 144
- # of articles excluded  n = 858

# of articles with data collected  

n = 157 (92 + 65 from original search†)

# Cohort or cross-sectional design††  

n = 143

# Case control design  

n = 5

# Ecological††  

n = 10

†“Original search” refers to the search for the systematic review conducted in 2011
* Two articles reported on two study populations each
†† One article reported ecological as well as individual-level data

### Records identified through database searching:
- EMBASE  n = 13,408
- MEDLINE  n = 10,013
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  n = 10

†“Original search” refers to the search for the systematic review conducted in 2011
* Two articles reported on two study populations each
†† One article reported ecological as well as individual-level data
Appendix 3: Flow Diagram for Paediatric Burden Systematic Review
Appendix 4: Flow Diagram for Paediatric Burden Systematic Review

* Yates et al., 2010 (11) and Pierce et al., 2011 (12) used the same study population, the former representing an earlier version of the study, published before full follow-up of pregnancy outcomes had been completed. Only the Pierce study has been retained in this review.
Appendix 6: Key Parameters Reviewed by the Taskforce

**Children and Pregnant Women Influenza Disease Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Children &lt; 6 months of age</th>
<th>Pregnant Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>influenza attack rate (infection)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>influenza attack rate (symptomatic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza-associated hospitalization rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza-associated mortality rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>influenza disability adjusted life years lost</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vaccine effectiveness to prevent symptomatic influenza virus infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vaccine effectiveness to prevent influenza-associated hospitalizations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vaccine effectiveness to prevent influenza-associated mortality</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Definitions of symptomatic infection and hospitalization may differ between studies. The Taskforce will recommend how to best reconcile differences in study design when recommending parameter estimates.

2. It is anticipated that there will be very little high quality data available to the Taskforce to recommend estimates for these parameters. Extraploations from existing evidence may be necessary.

3. Note that a key objective of this Taskforce is to highlight areas where existing data quality can be improved and important research needs still needs to be done. For parameters such as influenza DALYs lost, it is expected that there will be very little data, yet this parameter is important to compare influenza prevention programs with other important public health interventions.
## Fetus Influenza Disease Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fetuses/birth outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>influenza-associated prematurity rate(^1)(^2)</td>
<td></td>
</tr>
<tr>
<td>influenza-associated small for gestational age rate(^1)(^2)</td>
<td></td>
</tr>
<tr>
<td>influenza-associated loss of pregnancy(^1)(^2)</td>
<td></td>
</tr>
<tr>
<td>influenza disability adjusted life years lost(^2)</td>
<td></td>
</tr>
<tr>
<td>vaccine effectiveness to prevent prematurity(^2)</td>
<td></td>
</tr>
<tr>
<td>vaccine effectiveness to prevent SGA birth(^2)</td>
<td></td>
</tr>
<tr>
<td>vaccine effectiveness to prevent loss of pregnancy(^2)</td>
<td></td>
</tr>
</tbody>
</table>

1. Definitions of prematurity, SGA, and pregnancy loss may differ between studies. The Taskforce will recommend how to best reconcile differences in study design when recommending parameter estimates.
2. It is anticipated that there will be very little high quality data available to the Taskforce to recommend estimates for these parameters. Extrapolations from existing evidence may be necessary.
3. Note that a key objective of this Taskforce is to highlight areas where existing data quality can be improved and important research needs still needs to be done. For parameters such as influenza DALYs lost, it is expected that there will be very little data, yet this parameter is important to compare influenza prevention programs with other important public health interventions.
Appendix 7: Taskforce Participants

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20. Helen Marshall University of Adelaide, Australia
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