

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. This report is written by the Taskforce Chair, Bradford Gessner (AMP), the Workstream Leads are Niranjana Bhat (PATH), Deshayne Fell (McGill University), and Mark Loeb (McMaster University), and the Taskforce Rapporteur, Mark Katz (Independent Consultant).

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.

The full Interim Report of the **WHO Taskforce to Evaluate Influenza Data to Inform Vaccine Impact and Economic Modelling** can be found at the IVR website:

http://www.who.int/immunization/research/meetings_workshops/taskforceinterimreportMarch2015/en/