Influenza vaccination in pregnancy: careful assessment confirms safety concerns for the offspring

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Valid evidence does not support universal influenza vaccination for pregnant women, the LTE objections are unfounded. The observational evidence is less valid than that from RCTs: important safety signals in all the RCTs require high consideration. In RCTs, influenza vaccinated women have mostly local adverse effects, while their offspring shows a nonsignificant excess of deaths, and a significant excess of serious presumed/neonatal infections in the larger RCT. Several Authors have financial relationships with vaccine producers, several conclusions omit the safety signals. A cited systematic review has methodological problems and excluded important published RCTs. Waiting for new independent RCTs, the precautionary principle suggests avoiding to promote pregnant women vaccination. Health services could offer it highlighting existing uncertainties, with balanced informations allowing informed choices.

I have not raised the problem of an excess of maternal deaths, and I reported that the two vs zero maternal deaths in the influenza vaccine and control groups in the South African trial are balanced by the three vs five maternal deaths in the Nepalese trial. The vaccinated mothers showed only an excess of local adverse effects: it should be considered significant without any doubt for the explained reasons.

Instead, my point was that deaths in the offspring of influenza vaccinated mothers (sum of reported stillbirth, death in the first week and infant deaths up to 175 days after birth) were always in tendency higher vs the offspring deaths in the control groups. Moreover, the trial in Mali showed also a significant excess of serious presumed/neonatal infections (the overall picture is summarized in Table 1).

The pre-specified protocol for the pooled analyses includes plans to evaluate safety outcomes in mothers and infants, with a particular focus on those outcomes that were too rare to be assessed in individual trials. These analyses are in progress and will contribute additional important evidence on this subject.

Good. Waiting for new evidence, the precautionary principle should suggest to avoid the promotion of a universal vaccination of pregnant women, even more so affirming that the offspring of unvaccinated mothers could have severe consequences, when the available trials show that the opposite could be true.

5) «the author’s assertions that RCT investigators had conflicts of interest due to receipt of prior support from vaccine manufacturers is unjustified. Many large vaccine studies conducted throughout the world are funded by the manufacturers of vaccine».

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Reply Letter to: Fell DB, Omer SB and Edwards KM. Influenza immunization during pregnancy: toward a balanced assessment of safety evidence. Hum Vaccin Immunother 2019.
This is precisely one of the conditions that constitute a conflict of interest. Therefore, my assertion that “the principal investigator (was) in financial relationships with the vaccine producer, and two authors with other influenza vaccine producers”\textsuperscript{2} in the South African trial, and that “many authors (were) in financial relationships with the sponsor or with vaccine producers”\textsuperscript{2} in the Nepalese trial, is justified.

6) «the resultant data are presented in a transparent and comprehensive manner in peer-reviewed journals, with full disclosure of any potential conflicts of interest.»

I am not always sure of this. E.g. the abstract of the trial in Mali\textsuperscript{5} states that “adverse events rates... were similar among groups”. It does not clearly state that the more common “presumed neonatal infections” were not \textit{generic}, but \textit{serious} adverse events. Summing them with the infant deaths (52 vs 37 in the control group), the resulting numbers of these serious or fatal events clearly crossed the statistical significance. The Abstract conclusion was:\textsuperscript{5} “Vaccination of pregnant women in Mali... was technically and logistically feasible and protected infants from laboratory confirmed influenza for 4 months”. This could have satisfied the sponsor’s expectations, but I doubt that it is a transparent and comprehensive manner to present the resultant data.

7) «independently conducted systematic reviews of the now large body of international evidence have not found any indication of increased risk of adverse maternal or infant health outcomes.\textsuperscript{10b}

This assertion is surprising. I have limited my assessment to the most recent of the cited references, a systematic review, published in 2018.\textsuperscript{6}

Although stating that “Publications after May 2017 were not included”, the review does not include two\textsuperscript{5,7} of the three trials already published (the fourth\textsuperscript{4} was published in September 2017), presumably because they were not placebo-controlled but active-controlled.

However, this exclusion has precluded important additional information. Even more so, because both Omer and the principal investigators of the three cited main trials\textsuperscript{3–5} have published in 2015\textsuperscript{8} “Method and expectations of these three large randomized trials supported by the Bill & Melinda Gates Foundation, which “are likely to strengthen the evidence base regarding the impact of influenza immunization in pregnancy”. Moreover, the review’s Authors\textsuperscript{6} included “cohort, case-control, cross-sectional, randomized controlled clinical trials”, but their meta-analyses have not distinguished the studies based on the design; in particular they analyzed the unique included RCT together with the different observational studies. This is a methodological error.\textsuperscript{9}
Incidentally, the study\(^8\) raises also some doubts about the previous statement in point (6): “the resultant data are presented... in peer-reviewed journals, with full disclosure of any potential conflicts of interest”. Indeed, in this study, published in 2015 in a peer-reviewed journal, the conflict of interest statement of the Authors was “None”. However, for example, the disclosure of the principal investigator of the South African RCT,\(^3\) published in 2014, was “receiving lecture fees and fees for serving on advisory boards from GlaxoSmithKline, Pfizer, and Sanofi Pasteur and grant support from Novartis, GlaxoSmithKline, Pfizer, Sanofi Pasteur, and MedImmune”.

8) “Given the substantial evidence of efficacy and safety of maternal immunization – including from four RCTs – a sufficient clinical equipoise does not exist. Therefore, it would be unethical to conduct further maternal influenza vaccine RCTs unless a substantially different vaccine is developed.”

I disagree. Given the alarming safety signals, coming precisely from the four RCTs, for possible life-threatening events in the offspring of influenza vaccinated pregnant women, I think that further RCTs with appropriate study designs are needed before promoting universal influenza vaccination in pregnancy. They should be carried out by independent bodies and researchers, and safety concerns should be largely dispelled before promoting universal seasonal influenza vaccination during pregnancy. In the meantime, health services could offer the vaccination in the second and third trimester, but without hiding the uncertainties still existing, and promoting a balanced information and a really informed choice.\(^10\)

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There are no conflicts of interest to disclose.

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