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REPLY LETTER

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

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ABSTRACT

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.

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Influenza vaccination; pregnant women; healthy vaccinee bias; Cochrane systematic review; serious adverse events; offspring deaths

The Authors of the Comment[1] raise several objections, listed below, with a corresponding reply.

1) «RCTs are not necessarily statistically powered to evaluate rare safety outcomes, and they do not reflect the "real-world" environment; thus, alternative study designs are required for complementary assessment of less frequent and/or adverse outcomes…».

This argument is usually used for the opposite purpose. That is to claim that the RCTs are too short, with wide exclusion criteria and insufficient number of participants, unable to identify uncommon or rare adverse effects. For this reason, their more punctual detection requires observational studies and pharmacovigilance systems.

Even more so, when even the trials show important safety signals, these should be taken immediately into great consideration.

2) «The author proposes that observational studies should be excluded from effectiveness and safety assessment because of bias introduced by self-selection of vaccination by healthier women».

I didn't say that. I argued that evidence from observational studies in pregnancy is subjected, among others, to the healthy-vaccinee bias. This tends to overestimate the vaccine effectiveness and safety. Therefore, to promote a preventive pharmacological intervention, more so in the vulnerable period of pregnancy, public health services should not rely only nor primarily on observational evidence.[2] Even more so if the (insufficient) evidence from the existing RCTs goes in tendency in an opposite and alarming direction.

3) «the author reported a risk ratio for maternal death based on two deaths in the vaccination group and none in the placebo group, resulting in a 95% confidence interval… too wide to be meaningfully interpretable».

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[3] are balanced by the three vs five maternal deaths in the Nepalese trial.[4] The vaccined mothers showed only an excess of local adverse effects: it should be considered significant without any doubt for the explained reasons.[2]

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[5] showed also a significant excess of serious presumed/neonatal infections (the overall picture is summarized in Table 1).

4) «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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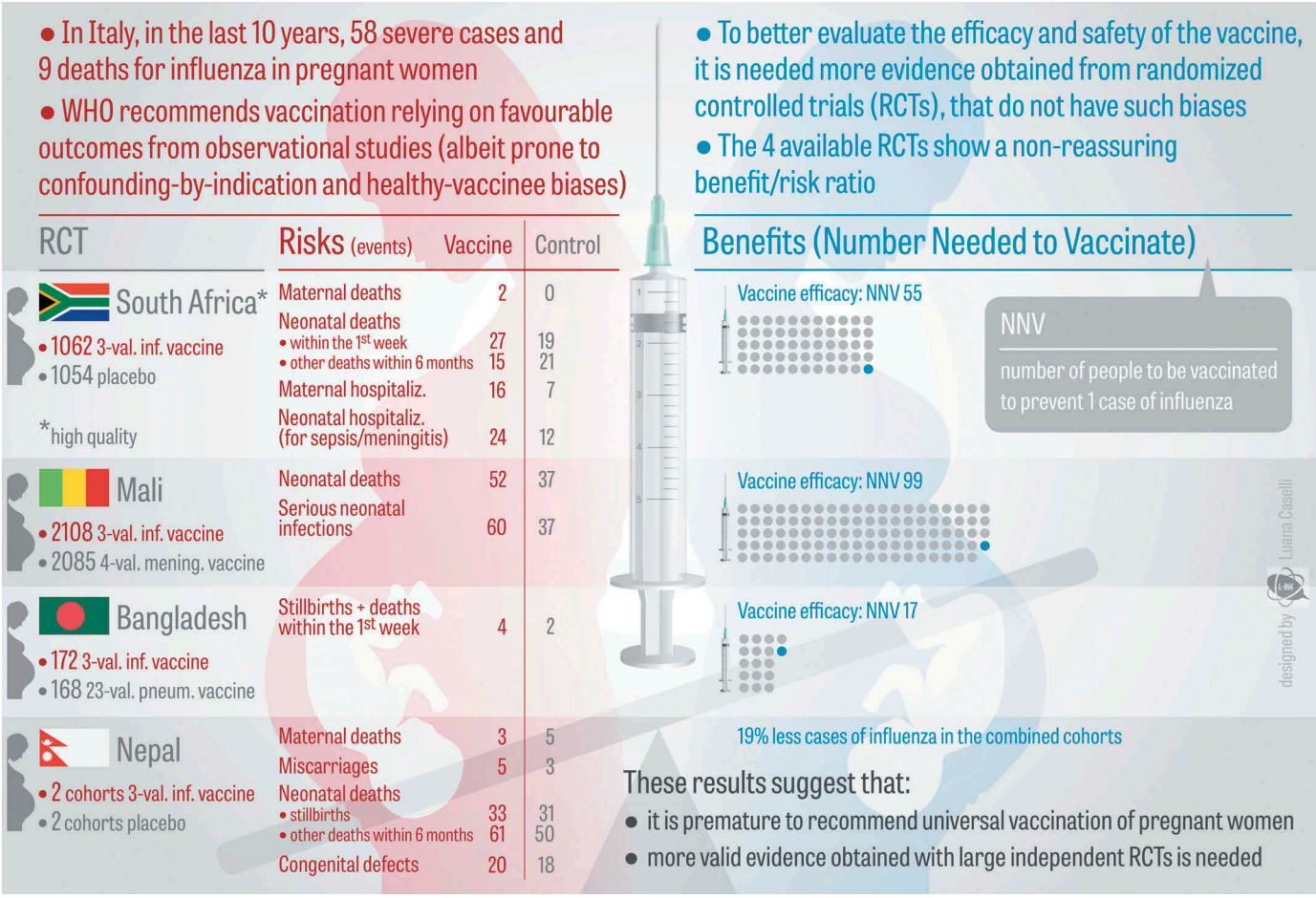
Reply Letter to: Fell DB, Omer SB and Edwards KM. Influenza immunization during pregnancy: toward a balanced assessment of safety evidence. Hum Vaccin Immunother 2019.

Table 1. Influenza vaccination during pregnancy: what evidence?



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"[2] in the South African trial, and that "many authors (were) in financial relationships with the sponsor or with vaccine producers"[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[5] states that "adverse events rates… were similar among groups". It does not clearly state that the more common "presumed neonatal infections" were not *generic*, but *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:[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.[10]»

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

Although stating that "Publications after May 2017 were not included", the review does not include two[5,7] of the three trials already published (the fourth[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,[3–5] have published in 2015[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[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.[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]

Disclosure of potential conflicts of interest

There are no conflicts of interest to disclose.

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References

1. Fell DB, Omer SB, Edwards KM. Letter to the editor on KHVI-2018-0464. in press. Human Vaccines & Immunotherapeutics.
2. Donzelli A. Influenza vaccination for all pregnant women? So far the less biased evidence does not favour it. Hum Vaccin Immunother January. 2019:1–6. doi:10.1080/21645515.2019.1568161.
3. Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, Adrian PV, van Niekerk N, Treurnicht F, Ortiz JR, et al.; Maternal Flu Trial (Matflu) Team. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med. 2014;371:918–31. doi:10.1056/NEJMoa1401480.
4. Steinhoff MC, Katz J, Englund JA, Khatry SK, Shrestha L, Kuypers J, Stewart L, Mullany LC, Chu HY, LeClerq SC, et al. Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebocontrolled trial. Lancet Infect Dis. 2017;17:981–89. doi:10.1016/S1473-3099(17)30252-9.
5. Tapia MD, Sow SO, Tamboura B, Tégueté I, Pasetti MF, Kodio M, Onwuchekwa U, Tennant SM, Blackwelder WC, Coulibaly F, et al. Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial. Lancet Infect Dis. 2016;16:1026–35. doi:10.1016/S1473-3099(16)30054-8.
6. Giles ML, Krishnaswamy S, Macartney K, Cheng A. The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review. Hum Vaccin Immunother. 2018 October;1–13. doi:10.1080/21645515.2018.1540807 [Epub ahead of print].
7. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, Omer SB, Shahid NS, Breiman RF, Steinhoff MC. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med. 2008;359:1555–64. doi:10.1056/NEJMoa0708630.
8. Omer SB, Richards JL, Madhi SA, Tapia MD, Steinhoff MC, Aqil AR, Wairagkar N. for the BMGF supported maternal influenza immunization trials investigators group. Three randomized trials of maternal influenza immunization in Mali, Nepal, and South Africa: methods and expectations. Vaccine. 2015;33:3801–12. doi:10.1016/j.vaccine.2015.05.077.
9. Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Cochrane handbook for systematic reviews of interventions. Higgins JPT, Green S, editors. Basel, Switzerland: Wiley-Blackwell; 2011. ISBN 978-0-470-69951-5 PG 396.
10. Donzelli A. Influenza vaccinations for all pregnant women? Better evidence is needed. Int J Environ Res Public Health. 2018;15:2034. doi:10.3390/ijerph15092034.