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COMMENTARY

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Influenza vaccination for all pregnant women? So far the less biased evidence does not favour it

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ABSTRACT

Pregnant women are a WHO priority group for influenza vaccination, but evidence from observational studies in pregnancy is subject, among others, to the healthy-vaccinee bias, overestimating the vaccine effectiveness and safety. An USA survey adds new evidence that documents this bias. Therefore, it is essential to assess vaccine effectiveness and safety with RCTs. Cochrane reviews identified one RCT with "low risk of bias", in a medium-income country, with NNV 55 for mothers. Its data show an excess of local adverse effects, and a tendency to harm for serious adverse events, with uncertain or very limited protection against influenza. A subsequent larger trial in a very-low-income African country found an excess of infant serious infections plus deaths in the influenza vaccine group. Also an available previous small trial and a subsequent large one in Asian low-income countries showed in tendency more deaths in the offspring vaccine groups. Before promoting seasonal influenza vaccinations during all pregnancies, more independent trials are needed, with appropriate designs and comparators. Meanwhile, vaccination in second-third trimester could be offered communicating the uncertainties and promoting informed choices, without neglecting to promote other protective behaviors.

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Introduction

The Health Systems increasingly recommend flu vaccination for all pregnant women.

The World Health Organization (WHO)[1–3] recommends it regardless of the stage of pregnancy, claiming that pregnant women are the priority group for annual vaccination, due to their greater susceptibility to severe influenza from the second trimester to the postpartum period. An argument is that 5% of influenza-related deaths in the 2009 pandemic happened during pregnancy, despite the pregnant women representing only 1% of the total affected population.[4]

The Italian National Health Service recommends seasonal vaccination for women in the second and third trimester of pregnancy at the beginning of the epidemic season.[5] The above reason[4] is frequently cited, even though over the last ten years the deaths in Italian pregnant women have been nine, about 1% of the total influenza-related deaths.

The available evidence about the adverse effects of influenza and influenza vaccinations in pregnant women and their babies relies almost exclusively on observational studies.

A systematic review of safety outcomes (fetal death, spontaneous abortion, congenital malformation) associated with influenza vaccination during pregnancy[6] included 1 case-control, 1 cross-sectional and 17 cohort studies, but no randomized trials (RCTs), though citing one of them.

I have recently re-discussed the evidence about the recommendation of universal influenza vaccination in pregnancy,[7] concluding that better evidence is needed about its safety.

Objective

The objective of this work is to analyze new observational evidence, that provides plausible alternative explanations for the benefits in newborns of vaccinated pregnant women; and to add new evidence from the available RCTs, supporting the assertion that better evidence is needed about the safety of influenza vaccination during pregnancy.

Evidence from observational studies

Observational studies are prone to bias, specifically to confounding-by-indication and to healthy-vaccinee bias. The former concerns patients with underlying diseases, who are more likely to be vaccinated than healthy people; this bias leads to underestimate the vaccine effectiveness, because the less healthy population is inherently at higher risk of unfavorable health outcomes. The second bias refers to an opposite situation, where patients in worse health conditions (eg with functional impairment, other comorbidities, or the elderly with a short life expectancy) are less likely to adhere to the influenza vaccination. This is a variant of the so called "healthy-adherer effect", a bias associated with patient behaviour. It can affect health outcomes, that may be incorrectly attributed to the presence or absence of a treatment.

The subjects adhering to preventive treatments are usually more likely adherent to healthy lifestyles than subjects less adherent to treatments[8,9]. Aspects of a healthy lifestyle include healthier diet, physical activity/exercise, abstention from alcohol abuse, illegal drugs or risky behaviours, and seeking more

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health assistance, and of better quality. The good adherence can also be linked to more trust in the proposed health interventions, that may in turn lead to better outcomes. All these characteristics are typically not measured in pharmacoepidemiologic databases (some are impossible to measure), and may be associated with outcomes in observational studies.

The healthy-vaccinee bias leads to an overestimation of vaccine effectiveness and safety.

To test the residual confounding caused by healthy-vaccinee effects even in adjusted data, some authors obtained estimates for time periods before and after the influenza seasons.

A systematic study of the two cited forms of bias[10] showed that statistical adjustment for confounders was able to partially correct the confounding-by-indication bias. Nevertheless, many studies have continued to show an inexplicable significant vaccine effectiveness *before* and *after* the influenza season, with evidence of large residual confounding, postulating a healthy-vaccinee bias.

A previous study hypothesized that this bias might strongly operate in the setting of pregnant women.[7] Indeed, better educated and more health-conscious women, with general healthier behaviors and seeking better medical care, might be more adherent to this vaccination, increasingly recommended by doctors, professional societies, and public health authorities.[11] E.g, there is evidence that pregnant women receiving recommendations for the influenza vaccine from their obstetrician or obstetric provider are 5- to 50-fold more likely to be immunized.[11] Instead, pregnant women with a lower education and/or of foreign origin are less likely to be vaccinated,[12] and even to have any prenatal care.[13]

While in the elderly both confounding-by-indication and healthy-vaccinee bias coexists and may strongly operate in opposite directions, in pregnant women confounding-by-indication could be weaker and the healthy-vaccinee bias much stronger. A CDC recent report[14] have provided new convincing evidence of this objective bias. CDC analyzed data from an Internet panel survey conducted during March 28–April 10, 2018. Among 1,771 survey respondents pregnant during the peak influenza vaccination period, 49.1% reported receiving influenza vaccine.

Although this was a nonprobability sampling survey, the data are interesting anyway, and show that the women not vaccinated for influenza were: (Table 1)

- on one side somewhat less affected by "high risk diseases", which translated in slight less chance to be vaccinated: 46.3% versus 54.0% (that is 7,7% absolute points difference),
- on the other side, they were heavily disadvantaged from every educational and socio-economic point of view. Among the unvaccinated women were over-represented those black, less educated, unmarried, without insurance, not working, below poverty, with no or few provider visits… Any of these conditions was associated with a much larger gap in the chances of not receiving an influenza vaccination. It is quite likely that the worse socio-economic and educational conditions of these mothers could explain the poorer outcomes of their children, without having to invoke the explanation of a missed vaccination.

Table 1. Influenza coverage among pregnant women, by selected characteristics – Internet panel survey, United States, april 2018 [14, simplified.](Women pregnant any time during October–January were included in the analysis to assess influenza vaccination coverage for the 2017–18 season. Women who received an influenza vaccination since July 1, 2017, before or during their pregnancy were considered vaccinated).

Characteristic	Vaccinated, weighted %
Race/Ethnicity (self reported)	
White, non-Hispanic[¶]	52.5
Black, non-Hispanic	35.6[§]
Hispanic	51.3
Other, non-Hispanic	53.0
Education	
≤High school diploma	41.8[§]
Some college, no degree	40.0[§]
College degree	56.0
>College degree[¶]	59.7
Marital status	
Married[¶]	56.9
Unmarried	38.8[§]
Insurance coverage	
Private/Military only[¶]	55.3
Any public	44.2[§]
No insurance	30.1[§]
Employment status	
Working[¶]	53.5
Not working (out of work, homemakers, students, retired, or unable to work)	43.9[§]
Poverty status	
At or above poverty[¶]	52.0
Below poverty	38.8[§]
High-risk condition (diseases associated with increased risk for serious medical complication from influenza)	
Yes[¶]	54.0
No	46.3[§]
No. of provider visits since July 2017	
None	18.1[§]
1–5	37.4[§]
6–10	49.9[§]
>10[¶]	56.8
Provider vaccination recommendation/offer	
Offered[¶]	63.8
Recommended with no offer	37.6[§]
Recommended with no offer, referral received	47.9[§]
Recommended with no offer, no referral received	30.1[§]
No recommendation	9.0[§]

[¶] Reference group for comparison within subgroups.
[§] ≥5 percentage-point difference compared with reference group.

Evidence from randomized controlled trials

For the above reasons, before recommending a universal vaccination, it seems logical to require also strong and consistent evidence from RCTs. Indeed, the Bill & Melinda Gates Foundation (BMGF) funded three large studies to confirm these requirements in low-resource settings.[15]

Two Cochrane Systematic Reviews[16,17] assessed the impact of influenza vaccination during second-third trimester of pregnancy on maternal, neonatal, and infant health outcomes compared to placebo/control, finding only one RCT of high validity, at "low risk of bias".

The Matflu (in South Africa)

The trial was funded by BMGF and by public sponsors, with the principal investigator in financial relationships with the vaccine producer, and two authors with other influenza vaccine producers.[18] The main findings, highlighted in a former article,[7] focused on the main group of the HIV-uninfected mothers: 1062 vaccine vs 1054 control group. The vaccine

group showed a slight decrease in confirmed influenza (number-needed-to-vaccinate [NNV] 55 and 56 for mothers and infants, respectively), while some not significant differences in adverse events showed not reassuring tendencies. Indeed, as reported without comments in a Cochrane Review of 2015,[16] there were two maternal deaths in the vaccine group and no death in the placebo group (RR 4.96; 95% CI 0.24–103.24, moderate quality evidence). The perinatal deaths (stillbirths and deaths in the first week of life) were 15 and 12, in total 27, in the vaccine group; and 9 and 10, in total 19, in the placebo group (RR 1.32; 0.73–2.38, moderate quality evidence). The infant deaths up to 175 days after birth showed an apparent catch up: 15 in the vaccine group, and 21 in the placebo group (RR 0.71; 0.37–1.37, moderate quality evidence). There could be room to speculate that the modest/moderate inflammatory stress linked to vaccination[19-21] might not be benign for some predisposed and frail fetuses, anticipating unfavorable outcomes to some extent.

There were no differences in terms of influenza-like illness in women (RR 0.96; 0.79–1.16) or their babies (RR 1.02; 0.94–1.09), or of any respiratory illness in women (RR 0.97; 0.91–1.04, high quality evidence) or their babies (RR 1.01; 0.95–1.07, high quality evidence). Adopting a *patient* and *community oriented* perspective, the one that matters to people, and that should also matter to public health experts proposing universal public health interventions, a reduction in a vaccine-specific infection is of limited value, if the *net* burden of influenza-like illness (including the true illness from influenza virus) does not decrease.

Moreover, the trial[18] and the review[16] did not find significant differences between the two groups in terms of more serious adverse events: maternal hospitalization for any infection (RR 2.27; 0.94–5.49; moderate quality evidence), and neonatal hospitalization for sepsis (RR 1.60; 0.73–3.50; moderate quality evidence). However, while the differences for these two outcomes did not reach statistical significance, their tendencies were not in the expected/hoped direction. In fact, maternal hospitalizations for any infections were numerically higher in the vaccinated women: 16/1062, vs 7/1054 in controls. Also the presumably more severe neonatal infections, hospitalization for sepsis in the first 28 days of birth and meningitis, were numerically higher: 16 + 6/1026, vs 10 + 2/1023 in controls, although the difference was not statistically significant (RR 1.83; 0.91–3.67).

The effect against the target virus was modest, even in this pragmatic trial in Soweto, where probably the demographic structure of the population and the number of family members may facilitate the spread of the infection compared with high-income countries. Moreover, the influenza infections are often included in the broader term influenza-like illness [ILI], and for ILI no differences were apparent. Even if they were not included within ILI in Matflu, the RR of 0.50 for RT-PCR confirmed influenza translated only in 18 less influenza illnesses in vaccinated mothers and their children,[16] to be weighted (see above) against 9 more maternal hospitalization for any infection and 6 more neonatal hospitalization due to sepsis within 28 days of birth.

Finally, the RCT[18] reported that "Injection-site reactions (mainly mild to moderate) were more frequent among vaccine recipients than among placebo recipients in both cohorts, but there were no other significant differences in solicited reactions between the two study groups in either cohort.". However, this assertion is highly debatable.

Indeed, local (and systemic) reactions showed a clear disadvantage for the vaccinated women, and indeed the difference in these reactions is statistically significant, because a proper control group should have *no injection* (and consequently no small local trauma, nor nocebo effect, always possible in a double-blind RCT, in which patients and study personnel are unaware of whether the injection contains an active drug). And *no injection* would mean "no tenderness, no induration, no bruising, no severe reactions" in the site of a "no injection", nor any nocebo effect.

Moreover, some local reactions were defined as severe: at least one severe reaction occurred in 5% of vaccinated, that is an excess of about 53 severe local reaction (versus 18 less influenza illnesses), provided that a fair control group should have "no reaction in the point of no injection".

Finally, also for systemic reactions for which a control group has a natural background rate (weakness, tiredness, fever, joint pain) the vaccinated group showed a tendency to more severe reactions, even not taking into account the potential nocebo effect of participant unaware if they received only a saline injection. Note that these biases are common in the *placebo*-controlled vaccine trials, and that they are greater when the so-called *placebo* group is injected with an adjuvant, not to say of control groups active-controlled with *other vaccines*.

Evidence from a subsequent large RCT (in Mali)

An updated Cochrane Review on vaccines for preventing influenza in healthy adults[17] added to the aforementioned[18] another large RCT, active-controlled, observer-blind, assessing the efficacy of influenza vaccine (pH1N1) in third-trimester pregnant women.[22] Also this trial was funded by BMGF, and the Authors declare no competing interests. The participants were randomly assigned to receive trivalent inactivated influenza vaccine (n = 2108) or quadrivalent meningococcal vaccine (n = 2085). The primary outcome was the first case of laboratory-confirmed influenza in infants by age 6 months. In the intention-to-treat population, overall infant vaccine efficacy was only 33.1% (95% CI 3.7–53.9), and 37.3% (7.8–57.8) in the per-protocol population. Vaccine efficacy remained robust during the first 4 months of follow-up, then declined. Adverse event rates in women and infants were "similar among groups. Pain at the injection site was more common in women given quadrivalent meningococcal vaccine (…) reactions were mild.".[22] The Authors conclusion was: "Vaccination of pregnant women with trivalent inactivated influenza vaccine in Mali – a poorly resourced country with high infant mortality – was technically and logistically feasible and protected infants from laboratory confirmed influenza for 4 months.".

Unfortunately, although reporting that "(serious) Presumed/neonatal infection was more common in infants in the trivalent inactivated influenza vaccine group than in those in the quadrivalent meningococcal vaccine group (n = 60 vs n = 37; p = 0.02).", the Authors stated that "No serious adverse events were related to vaccination.".[22] However, this statement is very questionable, since randomisation should ensure the best comparability between the study groups and control of the confounding factors. Therefore it should allow to admit a causal relationship between treatment and observed effects.

Moreover, also the infant deaths were in tendency higher in the influenza vaccine group (52 vs 37, RR 1.39; 95% CI 0.92–2.11; P = 0.122). These deaths only partially overlap with the 97 (60 + 37) serious presumed/neonatal infections, because 77 of these infants survived (personal communication of the Author). Therefore, summing the infant deaths to the cases of serious infections not hesitated in death in each group, the disadvantage of the group with influenza vaccination becomes significant.

Evidence from a previous small RCT (in Bangladesh)

Another active-controlled much smaller RCT[23] assessed the efficacy of influenza vaccination in pregnant women, assigning 172 mothers to inactivated influenza vaccine (influenza group) and 168 to the 23-valent pneumococcal polysaccharide vaccine (control), in the third trimester of pregnancy. Also this study was funded by BMGF, a cooperative agreement with public bodies and Pharmaceutical Companies. The results showed fewer cases of laboratory-confirmed influenza in the influenza than in the control group (6 vs 16), with a vaccine effectiveness of 63%, and a reduction in respiratory illness with fever, with a vaccine effectiveness of 29% in infants. However, the infant deaths were compatible with the results of the above two trials: 3 stillbirth and 1 perinatal death in the influenza group, versus 2 perinatal deaths in the active-controlled group.

Evidence from a last large RCT (in Nepal)

This trial, funded by BMGF, with many authors in financial relationships with the sponsor or with vaccine producers, was implemented in two sequential annual cohorts of pregnant women 17 to 34 weeks of gestation, randomised (1:1) to seasonally recommended trivalent inactivated influenza vaccine or saline placebo.[24]

The immunisation significantly reduced maternal influenza-like illness (overall efficacy: 19% in the combined cohorts), influenza in infants aged 0–6 months (efficacy of 30%), low birthweight (by 15%). The adverse events were similar (i.e. not statistically different) in both groups, with five women deaths in the placebo groups and three in the vaccine, but:

- miscarriage in three (0,2%) participants in the placebo group, vs five (0.3%) in the vaccine group
- stillbirth in 31 (1.7%) in the placebo group, vs 33 (1.8%)
- congenital defects in 18 (1.0%) in the placebo group, vs 20 (1.1%)
- infant deaths at age 0–6 months: 50 in the placebo group, vs 61.

Again, the tendency in infants' adverse events was worse in the vaccine group. The Authors stated that no serious adverse events were associated with the immunisation, but this statement is questionable in an RCT, as already discussed.

Discussion

This review shows that the safety of influenza vaccinations in pregnant women and their babies relies essentially on observational studies (plus passive pharmacovigilance, which however tends to underreport adverse events, even serious ones, if they have a fairly high background rate). Unfortunately, observational studies are affected by bias, mostly the healthy-vaccinee bias, that can account for the asserted benefits for the vaccinated mothers and their offspring.

The Cochrane reviews[16,17] identify only one high-quality large placebo-controlled RCT, whose safety results are described as "no significant between-group differences"[18] in serious adverse events, despite the tendencies are not reassuring.

Two other RCTs compared influenza vaccination with meningococcal or pneumococcal vaccination in low-income countries. The first and larger trial[22] substantially disregarded an alarming excess of infant deaths and serious "presumed/neonatal infections" in the influenza vaccine group. Even in the other small RCT[23] the fetal plus infant deaths were nonsignificantly higher in the influenza vaccine group.

In a last large trial[24] the tendency for miscarriage, stillbirth, congenital defects, and infant deaths at 0–6 months were not in favour of the vaccine group.

These countries are not comparable to high-income ones, but one could expect that their poverty and demographic conditions would magnify the benefits of influenza vaccination, not the opposite.

The mechanism of hypothetical harms is unclear (an inflammatory stress linked to this vaccination[19-21], risky for some predisposed/frail fetuses?), but it seems clear the need of further RCTs with appropriate study designs. They should be carried out by independent bodies and researchers, and safety concerns should be dispelled before promoting universal seasonal influenza vaccination during pregnancy. These RCTs should be large and pragmatic, with proper comparison groups, including one in which the intervention is "to do nothing", and long-term follow-up. In the meantime, health services could offer the vaccination in the second-third trimester to pregnant women requesting it, after having received a really balanced information, to promote informed choices.

An usual objection is that "it would be unethical excluding the control group from the benefits of vaccination". This objection could be overcome randomizing only women persistently hesitant about vaccination, despite a comprehensive information on the existing evidence and uncertainty about potential benefits and risks.

In accordance to the precautionary principle, it seems reasonable to avoid the vaccination in the first trimester of pregnancy, unless an informed woman requests it. More so in high-income countries, where influenza harms to pregnant women and their fetuses might be less dramatic, and the probabilities of infection for a pregnant woman may be lower, because of the demographic structure of families and population.

This does not mean leaving them without defenses: many other protective measures can be implemented, to reduce infections and their most dramatic consequences, as explained elsewhere.[7]

Conclusions

In substantial agreement with the Cochrane reviewers[16,17], I think that further RCTs with appropriate study designs are needed for influenza vaccination in pregnancy. They should be carried out by independent bodies and researchers, and safety concerns should be dispelled before promoting universal seasonal influenza vaccination during pregnancy. Current evidence from valid studies is insufficient and not reassuring.

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