Author’s response to reviews

Title: Epidemiology of influenza in pregnant women hospitalized with respiratory illness in Moscow, 2012/2013-2015/2016: a hospital-based active surveillance study

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Point-by-point response:

Technical Comments:

1. Please include the full name of the ethics committee (and the institute to which it belongs to) that approved the study and the committee’s reference number if appropriate in the "Ethics Approval and Consent to Participate" subsection of the Declarations.

Authors: The ethics committee that approved this study is described in this section on page 17 of the manuscript, as follows:
“The study was approved by the “Ethics Committee of Hospital No.1 for Infectious Diseases”, CHID#1, Moscow Health Department, Russian Federation.”

2. Please add all the authors initials and contributions in the Author's Contributions section of your manuscript.

Authors: The contributions for each author are specified in this section on page 18 of the manuscript, as follows:

“L. Kisteneva, I.K., and L. Kolobukhina contributed to data acquisition and enrolling participants; S.T., E.Mukasheva, K.K., E.Morozova contributed to laboratory data testing, B.G., A.M., S.T. contributed to data processing, analysis, or interpretation; J.P. and E.B. provided overall study oversight and J.P. wrote the first draft of the manuscript.”

Editor Comments:

(None)

Reviewer reports:

Emilia Asuquo Udofia, MB.B.S., MPH, PhD (Reviewer 3):

Line 49, page 5: Why was the sample population limited to 15-44 years, and not perhaps 15-49 years? Any specific reasons for the selected range?

Authors: Dear Prof. Emilia Asuquo Udofia,

We thank you for reviewing our manuscript.

We restricted the analysis to women aged 15–44 years admitted with an acute respiratory infection because the number of admitted pregnant women 45 to <50 was small (just three admissions among 468 admissions of women 45 to < 50 years old).

In addition, the choice for the 15–44 years age range was to improve compatibility with previous publications, for instance:


We have now added this information to the ‘Study conduct’ section of the Methods.

Line 7, page 7 - delete 'included'

Authors: We agree and have deleted.

Lines 20 and 25, page 13; line 16, page 15 - should read "…. the present study…", not "current study"

Authors: We agree and have replaced the word “current” with “present” in these instances.

Jan Jaap H.M. Erwich (Reviewer 1):

The authors did not substantially addressed the remarks of ref 1 and 2 and changed the manuscript accordingly.

Authors: Dear Prof. Jan Erwich,
We are deeply grateful for your opinion concerning our work.

We have now made changes to the manuscript that address your previous comments below. These are marked in yellow highlighting in the revised manuscript.

This manuscript reports on a single center descriptive study on influenza in pregnancy.

The topic is of interest, and the description is sound and well written. However, I have two main questions:

Regarding the participation of this center in the Global Influenza Hospital Surveillance Network, and part of the authors are also authors on recent publications from this network (see their website),

1. I see no additional new information,

2. Why not publication of these results in a joint network publication as before? This will make the numbers much stronger and will omit some limitations the authors themselves note in the discussion. This is the core value of this network anyway.

Unless the authors can convince me otherwise, regarding 1, and 2, I see no urgency for separate publication of this manuscript.

Authors: Our investigation was conducted within the framework of The GIHSN Study that aims to generate data on the impact of influenza virus infection during hospitalization. The main goals of the investigation were (1) to estimate the incidences of all-cause acute respiratory illness and laboratory-confirmed influenza during hospitalization, (2) to examine the clinical spectrum of illness associated with influenza viruses and (3) to inform decisions about the value of influenza vaccination. We have made this clearer at the end of the Introduction section.

Our results and others show that pregnant women are at an increased risk for influenza-associated hospitalizations. We chose this population for a separate publication because little is
known about the incidence of influenza and influenza-associated complications during pregnancy in Russia. Never before have such data been published for the country. We believe, a separate publication is necessary and will allow us to focus public attention on this problem more closely.

During the work, data collection was carried out based on the standard GIHSN Protocol used by all countries participating in this network. This study was conducted only in one hospital, where there is a special Department for pregnant women with infectious diseases of the respiratory tract that is unique for Moscow (and also unique among other countries participating in the project). However, birth outcomes in pregnant women and data on born infants are not included in a standard Protocol and have not been published before anywhere. We additionally collected these data with the maximum possible completeness of the study within the framework presented in the publication. Finally, previous studies have usually included only small numbers of pregnant hospital admissions.

We have now justified these strengths in the Discussion, and describe how our data are new as follows:

“… the full burden of influenza in pregnant women and their infants is poorly understood due to differences in the design and conduct of epidemiological studies, and the small numbers of pregnant women included [21-23].

The present study describes new epidemiological data of influenza infection among a large cohort of pregnant women and the impact of influenza on clinical outcomes in these women and their infants. Using a prospective, active-surveillance study design as part of the GIHSN’s hospital-based surveillance [16], we collected data from more than 1700 pregnant women (825 with confirmed influenza) admitted to a hospital specializing in acute respiratory infections.

and, later in the Discussion:

“With more than 1700 pregnant admissions, this study provides important and detailed information about the impact of influenza in pregnant women that can be used to inform and support vaccination policies in this susceptible population. Furthermore, our study provides pregnancy outcome data, which are rarely included in epidemiological studies of influenza in pregnant women, and have not been published before.”

Regarding your second point, we would like to note that data from other countries (sites) would only slightly increase the size of the sample of observations due to the small number or lack of
similar observations in other participating countries. The number of pregnant woman included in all the other sites overall was less than 3% of all included patients. For instance, for the 2015/2016 season A total of 1051 women 15–45 years old were included in the study, of whom 615 were pregnant (596 in Moscow, 2 in the Czech Republic, 2 in Turkey, 4 in France, 3 in Valencia, 4 in India, and 4 in Curitiba (data submitted and pending publication).

This information is now described in the Discussion:

“…the unique nature of the CHID#1 study site allowed us to recruit a substantial number of pregnant women. CHID#1 receives the most pregnant admissions from any of the hospitals in the GIHSN network (over 97% of the total pregnant admissions based on unpublished GIHSN data from the 2015/2016 season).”

Therefore, because this study was unique in its large size and its outcome measures, combining the data with that from other GIHSN sites would be unlikely to substantially increase the sample size and could introduce more variability and distortion of the overall results.

We also believe that the data on morbidity among pregnant women, if combined with similar data obtained in the analysis of other population groups, can significantly distort the overall results. And it is not entirely correct to combine these results with data from other groups of the population due to the fact that pregnant women are a special risk group for morbidity and peculiarities of the course of pregnancy and infection.

At the same time, our data are unique and showed that not only the pandemic influenza virus, but also seasonal influenza viruses pose a threat to pregnant women, leading to a similarly high probability of hospitalization.

Therefore, the inclusion of these data in a separate publication is considered a necessary step to involve the public in the health of pregnant women and to call for the prevention of influenza through vaccination of pregnant women.

Eran Hadar (Reviewer 2):

Trashakova et al. explored the impact of influenza on pregnancy, neonatal outcomes. I think the study is nice, but some major concerns prohibit its publication at current form.
1) There is a selection bias, as hospitalization is a required criteria for study participation, there is an over-representation of pregnant women (as they more often hospitalized) in the population and overestimation of influenza as a consequence. These two populations - pregnancy and non-pregnancy, if hospitalized cannot be compared. A better comparison would be hospitalized pregnant women, due to acute respiratory illness - with and without influenza.

Authors: Dear Prof. Hadar, this study was conducted only in one hospital, where there is a special Department for pregnant women with infectious diseases of the respiratory tract. This is unique for Moscow (and also unique among other countries participating in the project). However, along with pregnant women, this hospital also takes patients belonging to other groups of the population (of all ages and both sexes). During the influenza epidemic season, the hospital receives all patients with signs of the respiratory disease. The number of adult non-pregnant women admitted to this hospital with influenza-like illness (ILI) is indeed lower than that of pregnant women with the same condition. This may be due to the probable lower number of admissions of non-pregnant women for medical care, and the rare need for treatment of non-pregnant women with ILI in a hospital. In addition, due to organizational issues adopted in Russia in the management of flows of patients with ILI, non-pregnant women with ILI are more often hospitalized in other hospitals of the city (not having specialized departments for the observation and treatment of pregnant women, patients with ARI, and primarily influenza).

Pregnant women are indeed hospitalized more often than the rest of the adult population, due to their increased vulnerability to acute respiratory infections. This allowed us to investigate the epidemiology of the disease in this population, in line with the study’s objective. Although on page 8 of the manuscript we present the odds of influenza in pregnant vs. non-pregnant women in the same study site (OR for influenza = 2.87 [95% confidence interval (CI), 2.10–3.92]; p < 0.001; data not shown), we want to clarify that the main comparative assessment and conclusions presented in the article were made by comparing hospitalized flu-positive pregnant women with hospitalized flu-negative pregnant women (see pages 9–13), i.e., the comparison you suggest. We have now added this potential selection bias to the limitations section of the Discussion:

“The main analysis was based on comparing hospitalized influenza-positive with hospitalized influenza-negative pregnant women. We were unable to compare pregnant admissions to non-pregnant admissions because of insufficient numbers of non-pregnant women, who are more frequently admitted for influenza-like illness to other hospitals in Moscow.”
2) The pregnancy outcome is not complete - as it was collected only if outcomes occurred during hospitalization?

Authors: Indeed, data on pregnancy outcomes could only be collected from pregnant women who had these outcomes during their hospitalization. This was because evaluating pregnancy outcome during the admission or during a follow-up until pregnancy termination was not in the study protocol. Nonetheless, we decided to include these important outcomes in the article, which are rarely included in epidemiological studies of influenza in pregnant women and have not been published before. Our team of authors made a unanimous decision to include them in the publication to attract the attention of colleagues to a deeper study of this issue.

We clarify this as a limitation in the Discussion section on page 15:

“Another limitation was that we could not assess the long-term effects of influenza on pregnant women, or pregnancy outcome beyond the current admission, because data were collected only from women while they were hospitalized, and follow-up evaluations until the end of pregnancy were not within the study protocol.”

3) As hospitalization is for acute respiratory morbidity, and influenza is detected only during hospitalization, then the risk for hospitalization is not influenced by influenza status rather by pregnancy status - i.e. risk for hospitalization is due to respiratory morbidity and not due to influenza, as it is not tested among non-pregnant women who are not hospitalized

Authors: As you rightly noted, the risk of hospitalization is affected by the coincidence of the positive values of the two criteria – pregnancy and the occurrence of acute ILI. In this regard, we believe, to assess this risk it is incorrect and impossible to compare the samples of pregnant women who were hospitalized for ILI with non-pregnant women who were not hospitalized for this reason. Also taking into account the features described by us in the response to your first comment, we did not have the opportunity to compare the incidence of influenza in pregnant women hospitalized for ILI, with a similar indicator among non-pregnant women, who in the course of ILI did not have indications for hospitalization (for observation and treatment). These limitations, as described above, are now better described in the Discussion of our manuscript.