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

Authors:
Svetlana Trushakova (s.trushakova@gmail.com)
Lidiya Kisteneva (lborisovna2007@yandex.ru)
Beatriz Guglieri-López (gugtriz@gmail.com)
Evgenia Mukasheva (mukasheva_evgeniya@mail.ru)
Irina Kruzhkova (irina-kru@yandex.ru)
Ainara Mira-Iglesias (amisqrt2@gmail.com)
Kirill Krasnoslobodtsev (kg_87@mail.ru)
Ekaterina Morozova (katerina.garina@gmail.com)
Ludmila Kolobukhina (lkolobuchina@yandex.ru)
Joan Puig-Barberà (jpuigb55@gmail.com)
Elena Burtseva (elena_burceva@mail.ru)

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Author’s response to reviews:

Dear Editor,

We submit our revised article “Epidemiology of influenza in pregnant women hospitalized with respiratory illness in Moscow, 2012/2013–2015/2016: a hospital-based active surveillance study” for publication in BMC Pregnancy and Childbirth.

We include a point-by-point response to the Reviewers’ comments below and highlight revisions in the manuscript, as required by the journal.
Thank you for the opportunity to revise our manuscript. We look forward to your decision.

Sincerely,

Svetlana Trushakova
Ivanovsky Institute of Virology
Ministry of Health of the Russian Federation
s.trushakova@gmail.com

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: We have now added the ethics committee that approved this study on page 15 of the manuscript.

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

Authors: We have now specified the contributions for each author on page 16 of the manuscript.

Editor Comments:

(None)
Reviewer reports:

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

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:

Dear Prof. Erwich,

We thank you for reviewing our manuscript. Our article describes new epidemiological surveillance of influenza infection among pregnant women, who are at particular risk of influenza-associated complications. The study was possible due to the study site’s participation in the GIHSN international influenza surveillance project and its use of the standardized and rigorous GIHSN protocols. Moreover, our study was based within a unique, specialized hospital department for pregnant women with infectious diseases, resulting in valuable and detailed information from a large number of pregnant women with confirmed influenza. Very few studies have investigated seasonal influenza spread and epidemiology among pregnant women, particularly on a large scale. Our study therefore provides new and important data 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.

The Moscow hospital at which this study was based receives by far 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 outcome measures), combining the data with that from other GIHSN sites would be unlikely to substantially increase the sample size. Moreover, combining the morbidity data with data obtained from smaller studies of influenza in pregnancy could introduce more variability and significantly distort the overall results. At the same time, because the data confirm that pregnant women are at increased risk from seasonal influenza A and B viruses, and that seasonal influenza has similar harm and spread in this population as pandemic influenza, the decision to publish these data separately rather than waiting for other sites’ (probably limited) data was considered important to immediately inform influenza vaccine policy and create awareness. For these reasons, a separate publication is necessary and could help focus attention on improving vaccination coverage among pregnant women in the near future.

Eran Hadar (Reviewer 2):

Trushakova 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,

We thank you for reviewing our manuscript.

The objective of our study was to describe the epidemiology of influenza in pregnant women and the impact of influenza on clinical outcomes in these women and their infants. The Moscow
hospital where this study was based was ideal to address this objective because it has a department specialized to receive pregnant women with infectious diseases of the respiratory tract. Consequently, the design of our study to include hospitalizations at this site was necessary to meet our objective, as very few other study sites can provide sufficient numbers of pregnant women with 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. In addition, on page 14 we mention the limitation that:

“only 244 non-pregnant women were included, which prevented us from comparing pregnant and non-pregnant admissions.”

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.

We clarify this as a limitation in the Discussion section on page 14:

“Because data were collected only from women while they were hospitalized, we could also not assess the long-term effects of influenza on pregnant women and their infants.”

We are working to overcome this limitation in the future.
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:

The study included admissions with ILI symptoms (admitted within 7 days of their onset) irrespective of pregnancy status and without previous knowledge of laboratory test results for influenza. The study only included hospital admissions because the main objective was to describe the epidemiology of severe cases of influenza (i.e., hospitalizations). Hence, per protocol, we cannot make inferences regarding non-hospitalized ILI cases.