**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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**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

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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: 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:

Emilia Asuquo Udoafia, 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?

Line 7, page 7 - delete 'included'

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

Authors:

Dear Prof. Emilia Asuquo Udoafia,

We thank you for reviewing our manuscript.

The main reason to choose the 15-44 age range was to improve compatibility with previous publications, for instance:


The last source used National Association for Public Health Statistics and Information Systems (available: www.naphsis.org. Accessed 2012 April 17) for recruiting pregnant women. “all women aged 15–44 years were selected according to childbearing age as defined by the National Association for Public Health Statistics and Information Systems”

We revised our manuscript to add the reference that conform to this age band.
Also we revised all amendments you noted in the manuscript.

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 deeply grateful for your opinion concerning our work.
Let us respond to your comments one more.

Our investigation was conducted in frames of The GIHSN Study that aims to generate data on the impact of influenza virus infection during hospitalization. The main goals of the investigation was 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.

Our results and others show that pregnant women are at an increased risk for influenza-associated hospitalizations. We chose this group of population for a separate publication, because little is known about the incidence of influenza and influenza-associated complications during pregnancy in Russia. Never before, such a data were published. 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.

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).

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 a pregnant woman with a high probability of being hospitalized and of being at risk similar caused by the pandemic strain.

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):

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,

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, along with pregnant women, this hospital also takes patients belonging to other groups of the population (of all ages and sex). 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 lower appeal of non-pregnant women for medical care, with a 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).

Precisely in terms of conditions of hospitalization, we are able to find out the etiology of acute respiratory infection. According to our data, about 50% of pregnant women hospitalized with signs of ILI had been confirmed influenza etiology of infection. This indicator (the proportion of influenza – positive variables) strongly depends on some factors: the duration of the disease before hospitalization, on the time of sampling from the onset of the disease, on the technical capabilities of laboratories and applied tests, as well as on the human factor. In this regard, we assume that the proportion of influenza cases among pregnant women is much higher. In addition, mainly due to hospitalization of a pregnant woman, we are able to identify the pathogen.

Based on foregoing, the main comparative assessment and conclusions presented in this publication were made by comparing hospitalized flu positive pregnant women with negative (pp. 9-13).
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 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.”

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).