Expert Review of Vaccines

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierv20

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To cite this article: Chittaranjan N. Purandare, Scott Preiss, Shafi Kolhapure & Sripriya Sathyanarayanan (2021): Expert opinion on the way forward for improving maternal influenza vaccination in India, Expert Review of Vaccines, DOI: 10.1080/14760584.2021.1932474

To link to this article: https://doi.org/10.1080/14760584.2021.1932474

Published online: 31 May 2021.

EXPERT REVIEW OF VACCINES
https://doi.org/10.1080/14760584.2021.1932474

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SPECIAL REPORT

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Expert opinion on the way forward for improving maternal influenza vaccination in India

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ABSTRACT

Introduction: : Rates of maternal vaccination against influenza are extremely low in India. An expert panel of obstetric–gynecologists and pediatricians met to develop consensus-based recommendations for improving awareness of the benefits of influenza vaccination during pregnancy in India.

Areas covered: : The group discussed experiences of influenza infection in pregnancy and infancy before focusing on maternal vaccination practices in India, including the degree of communication between obstetric–gynecologists and pediatricians and opinions on optimal timing for vaccination. The impact of inconsistent vaccine prescription practices by healthcare providers was discussed, as well as current clinical recommendations on maternal influenza vaccination.

Expert opinion: : Although clinical evidence demonstrates the benefit of maternal influenza vaccination in any trimester, influenza vaccination is not widely accepted in India as an integral part of antenatal care. There is a lack of familiarity among obstetricians of clinical guidelines on maternal influenza vaccination. This can be addressed with an education campaign targeting obstetricians and other providers of maternal healthcare. With variable influenza seasons between regions in India, common vaccine stock shortages, and data suggesting influenza vaccination is feasible anytime in pregnancy, all opportunities to offer vaccination to this high-risk group for severe influenza disease should be considered.

ARTICLE HISTORY
Received 22 December 2020
Accepted 17 May 2021

KEYWORDS
Expert testimony; India; influenza; influenza vaccination; maternal vaccination; pregnant women; timing

1. Introduction

The World Health Organization has recommended since 2012 that pregnant women be vaccinated against influenza at any stage of pregnancy [1]. This priority group recommendation, also adopted by other international and national healthcare organizations [2], is based on the substantial risk of severe influenza disease in this group. There is evidence that seasonal inactivated influenza vaccine is safe and effective in preventing influenza in pregnant women and young infants, in whom the disease burden is also high [3]. Despite this, vaccination rates in pregnant women are much lower than national targets in most countries [2].

In India, data suggest a high burden of maternal and fetal complications in pregnancy due to influenza [4–7]. A review of the literature showed influenza A/H1N1pdm09 infection increased maternal mortality by 25–75%, and is associated with greater disease severity when compared to non-pregnant women [6,8–10]. Maternal influenza infection also increased fetal mortality rate by 5.5–33% [4–6]. The Ministry of Health and Family Welfare in India recognizes pregnant women as a priority risk group for influenza vaccination [11] but maternal influenza vaccination rates remain as low as 0.0–12.8% [12–15]. Significant hurdles for the uptake of the vaccine include poor healthcare providers (HCP) practices and misconceptions regarding the safety and efficacy of the vaccine [13].

While clinical recommendations on influenza vaccination in pregnancy have been published by different medical professional organizations in India [11,16,17], none explore the reasons for low maternal vaccination rates in this country. To address this need, a panel of 11 obstetric–gynecologists and pediatric specialists from different regions of India (see Acknowledgments) met in February 2019 in Mumbai. This group of experts reviewed data on the influenza disease burden in India and discussed the issues that, in their opinion, should be addressed to improve awareness of the potential benefits of influenza vaccination during pregnancy and to increase vaccination coverage. Issues such as experience with disease, timing and practical factors influencing uptake of vaccination were discussed and analyzed in detail, and whenever there was a disagreement, a consensus based on majority was reached.

2. Expert group discussion

The expert panel set forth consensus-based recommendations to raise awareness and to increase uptake of maternal influenza vaccination, which are summarized below.

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Article highlights

- An expert panel of obstetric–gynecologists and pediatricians from different regions of India developed consensus-based recommendations for improving rates of maternal vaccination against influenza, which are extremely low in India.
- A major barrier appears be poor knowledge among obstetricians of the burden and severity of influenza infection in pregnant women; consequently, there are low levels of acceptance of the potential need for maternal influenza vaccination.
- Improved acceptance of maternal influenza vaccination may be facilitated by programs that encourage improved communication between pediatricians and obstetric–gynecologists.
- There is a clear need for wide dissemination of clinical guidelines and recommendations that recognize pregnant women as a high-risk group for severe influenza disease and the potential benefits of vaccination in any trimester of pregnancy.
- Misconceptions among patients surrounding maternal influenza vaccination need to be addressed with improved counselling of pregnant women plus better understanding of the factors associated with influenza vaccine acceptance and effective outreach in India.

2.1. Clinical experiences of influenza during pregnancy and early infancy

Clinical experiences of influenza in pregnancy shared by the expert panel highlighted the seriousness of infection, as manifested by severe morbidity, requiring prolonged stays in intensive care and advanced medical interventions. This is in line with global reports that include the considerable clinical data collected during the 2009 influenza A/H1N1pdm09 pandemic [18–20].

Experiences of cases of severe influenza in pregnancy prompted members of the expert panel to reinforce the practice of counseling patients on the benefits of vaccination against influenza as part of routine antenatal care. However, it was agreed that it was preferable for HCPs to feel motivated to offer vaccination before personally encountering a severe case of maternal influenza. Various studies have highlighted the importance of HCPs being proactive in recommending influenza vaccination to their pregnant patients [13,21–23]. In view of inconsistent vaccine prescription practices among HCPs in India, the expert panel agreed there is a need for improved awareness among clinicians of the seriousness of influenza in pregnancy. This can be supported with reinforced recommendations from medical professional bodies in India, such as the Federation of Obstetric and Gynecological Societies of India (FOGSI) [17] and the Association of Physicians of India [16].

The expert panel confirmed having regularly encountered cases of suspected viral illness in infants younger than 6 months of age and, with advances in diagnostics, confirmed cases of influenza in this age group. These early infancy cases tended to have severe influenza, as reported in this age group in other countries [19], likely due to immaturity of the immune system [3]. Since they are too young to be vaccinated, protection in this age group relies on transplacental transfer of antibodies from the mother [24] and various studies have demonstrated the effectiveness of maternal vaccination in preventing influenza infection in young infants [19].

The expert panel also recognized the increased risk of disease exposure for pregnant women who already have young children since influenza is a common pathogen in children under 5 years of age; there was an estimated 16 million influenza cases in this age group in India in 2016 [25]. Also, overcrowding, a major risk factor for respiratory infectious diseases, is common in India [26]; the estimated population density in India in 2018 was 455 people per square kilometer of land, compared to the global average of 60 [27].

2.2. Favorable safety profile of influenza vaccination during pregnancy

Various analyses of adverse event data found no evidence overall of an increased risk of adverse pregnancy outcomes following influenza vaccination in pregnancy [28–33]. Furthermore, influenza vaccine can be co-administered with tetanus-containing vaccines if the timings align, as recommended by the American College of Obstetricians and Gynecologists (ACOG) [34]. A retrospective cohort study of safety data from pregnant women in the Vaccine Safety Datalink showed concomitant administration of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis and influenza vaccines during pregnancy did not demonstrate a higher risk of adverse outcomes than sequential vaccination [35].

The expert panel noted that most of the safety experience is with trivalent influenza vaccines, with limited long-term safety data for quadrivalent vaccines (QIV), although QIV surveillance data continue to be analyzed and recent reports indicate no safety concerns [36,37]. The majority of currently available influenza vaccines are QIV, as noted in the latest recommendations on the control of seasonal influenza from the United States Advisory Committee on Immunization Practices [38].

2.3. Optimal timing for influenza vaccination in pregnancy

The optimal timing for maternal influenza immunization has not been established [39,40], and this was reflected by the wide variation in timing practiced by different members of the expert panel. This is partly because of differences between guidelines in recommended gestational age at time of vaccination. For example, the FOGSI recommends influenza vaccination from 26 weeks onwards, unless the risk of influenza is high, in which case the vaccine can be given earlier [17], while the ACOG [34] and Indian Chest Society and the National College of Chest Physicians of India [11] recommend vaccination at any time in pregnancy. This latter recommendation is supported by recent data from India, which suggested immunization with influenza vaccine in any trimester protected the mother and infant up to 6 months of age without evidence of significant maternal adverse effects [31].

Clinicians have been hesitant to administer influenza vaccines during the first trimester because of theoretical safety concerns that are not supported by clinical evidence [30,33]. First trimester of pregnancy is associated with a relatively high rate of spontaneous abortion. In a study comprising 800 women in India, the rate of early spontaneous abortion was reported to be 17.5% [41]. Thus clinicians expressed that

vaccination during the first trimester could lead to an erroneous belief among some patients that miscarriage can be caused by vaccination and contribute to misconceptions surrounding the safety of maternal influenza vaccination in the first trimester. This is likely to contribute to clinicians' hesitancy in prescribing the vaccine. A rationale for later vaccination is also supported by the fact that influenza disease occurs most frequently and is most severe in the second and third trimesters [42], indicating this as the period of highest susceptibility to disease complications. The panel noted that it takes about 2 weeks after vaccination for antibodies to develop in the body and provide protection against influenza infection, as such vaccination must be considered as early as possible [43]. It was also noted by some experts in the panel that misconceptions can be dispelled with proper counseling.

Taking all these factors into consideration, the expert panel agreed with timing vaccination after 12 weeks of gestation. To dispel any misconceptions at an early stage, HCPs should begin discussing influenza vaccination with patients in the first trimester, given the increased morbidity associated with influenza in later trimesters. The group also proposed that the recommended timing of vaccination in the FOGSI guidelines be updated to reflect the latest clinical evidence.

Optimal timing for maternal influenza vaccination may also be influenced by the expected seasonal peak of disease [19]. The peak influenza season is not uniform across India: an assessment of the timing of seasonal influenza epidemics in 2010–2017 found India had two large peaks separated by several months [44]. Local epidemiological data for influenza seasonality, rather than a hemisphere-based classification [1,45], need to be considered because India demonstrates a largely Southern Hemisphere pattern of seasonality, but with latitude-related subregional differences [11,46]. Taking these factors into consideration, the expert panel recommended a pragmatic approach, offering maternal influenza vaccination throughout the year with the vaccine formulation that is available at the time. This approach would avoid delaying vaccination in anticipation of a peak season that can vary by weeks or months from year to year. Waiting for a peak season could lead to lost opportunities to vaccinate and poor vaccine coverage, as well as sudden increases in demand during outbreaks and vaccine stock shortages as a consequence.

2.4. Communication between pediatricians and obstetric–gynecologists

The expert panel highlighted the fact that pediatricians and obstetric–gynecologists in India rarely come together to discuss influenza in pregnancy and recommendations for vaccination. The general opinion was that there is a need for pediatricians to take the lead in making obstetricians more aware of the risk of influenza in young infants, encouraging obstetricians to inform patients about the benefits of vaccination against influenza during pregnancy.

2.5. Impact of vaccine stock and administration practices, and government policies

In all regions of India, implementation of influenza vaccination tends to be reactionary to outbreaks [47]. Moreover, as in other resource-limited countries [18], supplies of influenza vaccines can be erratic, with availability for short periods, which can have an impact on the ability to offer vaccination year-round if the vaccine has not been stocked. Few obstetricians in India stock vaccines and, since this is not a routine practice, this specialism may lack knowledge of cold-chain requirements where vaccines are stocked. Instead, most obstetricians prescribe the influenza vaccine but it is usually administered by a general practitioner (GP). However, patients do not always present to the GP for vaccination.

The expert panel came to a consensus and recommended that obstetric–gynecologists vaccinate patients, rather than refer patients to their GP for vaccination. This strategy of administering influenza vaccination to pregnant women at the point of care for their pregnancy ensures that they receive the vaccine and the opportunity to vaccinate is not missed. This and other elements of maternal influenza vaccination can be supported by policies promoted by the government, although the expert panel agreed that, while helpful, government recommendations tend to lag behind those of medical professional bodies. In making policy decisions, the government takes guidelines from medical organizations into consideration. This underlines the importance of ensuring medical guidelines and recommendations reflect current clinical evidence.

3. Expert opinion

Clinical evidence supports the need for maternal influenza vaccination and presents a favorable safety profile for this approach. However, the consensus among this panel of experts is that maternal vaccination might not be widely accepted among obstetric–gynecologists in India and that a number of factors might contribute to this situation.

A major barrier is poor knowledge among obstetricians of the burden and severity of influenza infection in pregnant women and young infants and low levels of acceptance of the need for influenza vaccination, as evidenced by variable vaccine prescription practices among obstetricians that were reported by the expert panel and other published studies [12,13,15,48]. The panel also highlighted a lack of knowledge of optimal timing of vaccination among obstetricians or confusion about timing because of non-uniform recommendations from different medical professional bodies [16,17]. Moreover, in contrast to pediatricians, vaccination is not a routine practice for most obstetric–gynecologists in India. It follows that the latter may lack knowledge and confidence in certain aspects of vaccination, including patient counseling and consent, cold-chain requirements, and vaccine storage.

Improved acceptance of maternal influenza vaccination may be facilitated via programs that encourage improved communication between pediatricians and obstetric–gynecologists. There is also a clear need for better familiarity with national and regional clinical guidelines that recognize pregnant women as a high-risk group for influenza morbidity and mortality, and the potential benefits of vaccination in pregnancy. Since government policies are based on these documents, regular revisions are important, with an emphasis on new data from India on the burden of influenza in

pregnancy and young infants, the number of deaths mitigated by vaccination, vaccine efficacy, as well as data on the long-term risk profile of QIV in pregnancy. The guidelines most likely need to be disseminated more widely and should be accompanied by articles and editorials in the medical literature. These can be used to underpin education campaigns led by Indian medical professional bodies on the benefit of maternal influenza vaccination, targeting all stakeholders in maternal care, including obstetric–gynecologists, GPs, medical students, and newly qualified HCPs.

The expert panel also reported misconceptions surrounding maternal influenza vaccination among patients, such as beliefs that miscarriage can be caused by vaccination, the vaccine lacks effectiveness, and the disease is not severe. This may be due to ineffective communication with pregnant women about the benefits and risks of influenza vaccination [2,13,49,50]. Counseling of pregnant women needs to be comprehensive, covering the potential seriousness of influenza disease, influenza epidemics, and the impact of vaccines, including the protection offered to neonates. Dialogue-based interventions like social media and mass media can help disseminate information about the vaccine and reduce misinformation, thus decreasing vaccine hesitancy [51]. Moreover, effective outreach requires a better understanding of the factors associated with influenza vaccine acceptance among women in India [49,50].

Vaccine access and the cost of the vaccine are other obstacles to the successful implementation of maternal influenza vaccination [49,52]. Even though it is recognized widely as the most logistically feasible and cost-effective approach to decrease influenza morbidity in pregnant women and young infants, further cost-effectiveness studies may be necessary in resource-constrained countries [18], including India.

Strengths of this research include the generation of insights from an expert panel which consisted of obstetric–gynecologists and pediatric specialists from different regions of India who have several years of relevant real-life experience. Although care was taken to include pan-national and pan-cultural representation, the output is limited in generalizability for the whole Indian population. Despite this the panel provides several important insights to consider and successfully implement maternal influenza vaccination in India.

In conclusion, since pregnant women are a high-risk group for severe influenza disease, influenza vaccination should be considered an integral part of antenatal care. Over the next five to 10 years, it is imperative that obstetric–gynecologists, other HCPs, medical professional organizations, and public health bodies combine efforts to increase awareness of maternal influenza vaccination availability in India. Since clinical evidence suggests that the influenza vaccine can be administered in any trimester in pregnancy, any opportunity to vaccinate should be recognized.

Acknowledgments

Members of the Expert Group, Maternal Influenza Immunization, India: Dr. Anahita Chauhan (Seth GS Medical College & KEM Hospital, Mumbai), Dr. Amarjeet Chitkara (Max Super Speciality Hospital, Delhi), Dr. Krishnendu Gupta (Vivekananda Institute of Medical Sciences, Kolkata), Dr. Gayathri Kamath (Fortis Hospitals, Bangalore), Dr. Nidhi Khera (Apollo Specialty Hospital, New Delhi), Dr. Shyam Kukreja (Max Institute of Pediatrics, Patparganj), Dr. Jyotsna Mehta (City Hospital and Trauma Center, Lucknow), Dr. Rishma Pai (Lilavati, Jaslok, and Hinduja Hospitals, Mumbai), Dr. Bhaskar Pal (Apollo Gleneagles Hospital, Kolkata), Dr. Meeta Singh (Tanvir Hospital, Hyderabad).

The authors thank Dr. Anil Dutta (GSK, Medical Affairs, India) for his contributions towards the discussions. The authors also thank the Business & Decision Life Sciences platform for editorial assistance and manuscript coordination, on behalf of GSK. Benjamin Lemaire coordinated the publication's development and editorial support. Joanne Knowles (independent medical writer for Business & Decision Life Sciences) provided medical writing support.

Author contributions

All authors participated in the discussion and the development of this manuscript. All authors had full access to the data and gave final approval before submission.

Funding

GlaxoSmithKline Biologicals SA funded all costs associated with the development and publication of this manuscript.

Declaration of interest

S. Preiss, S. Kolhapure, and S. Sathyanarayanan are employed by the GSK group of companies. S. Preiss and S. Kolhapure, hold shares in the GSK group of companies as part of their employee remuneration. C. N. Purandare declares personal fees from GSK for advisory board membership. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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