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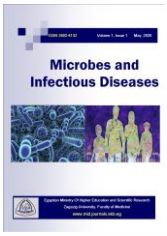

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Review article

The Effectiveness of maternal influenza vaccination in protecting neonates from respiratory infections

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ABSTRACT

Background: Maternal influenza vaccination is a vital public health strategy that safeguards both pregnant women and their newborns against severe respiratory infections. Influenza during pregnancy increases the risk of complications, including hospitalization and adverse neonatal outcomes. This review evaluates the effectiveness of maternal influenza immunization in reducing neonatal respiratory infections by enhancing passive immunity. It examines the mechanisms of transplacental antibody transfer, which provide early-life protection for infants who are highly susceptible to severe influenza-related complications. Evidence from clinical trials and large-scale vaccination programs demonstrates significant reductions in influenza-related morbidity among neonates born to vaccinated mothers. Despite these benefits, maternal influenza vaccine uptake remains suboptimal due to concerns about vaccine safety, limited awareness, and healthcare access barriers. Addressing these challenges requires targeted public health interventions, including educational campaigns, healthcare provider recommendations, and policy initiatives aimed at increasing accessibility and acceptance of maternal immunization. Strengthening global efforts to improve maternal vaccination coverage can substantially reduce the burden of neonatal respiratory infections, decrease healthcare costs, and enhance overall maternal and infant health outcomes. By reviewing current evidence and identifying strategies for improvement, this paper underscores the critical role of maternal influenza vaccination in protecting the most vulnerable populations.

Introduction

Influenza is a significant cause of morbidity and mortality worldwide, with pregnant women and neonates at heightened risk for severe complications [1,2]. Pregnant women experience various physiological changes, such as decreased lung capacity, increased cardiac output, and alterations in immune responses, which make them more susceptible to severe outcomes from influenza infection [3]. Furthermore, the immune system during pregnancy is modulated to prevent rejection of the fetus, leading to an increased vulnerability to infections, including influenza [4]. Influenza-related complications, such as pneumonia, can be particularly severe during pregnancy, and maternal hospitalization rates for influenza are substantially higher compared to non-pregnant women.

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Neonates are also particularly vulnerable to respiratory infections due to their immature immune systems. Influenza infection in neonates can lead to severe respiratory distress, hospitalization, and even death. As neonates cannot mount a robust immune response to influenza, their protection depends heavily on maternal immunity [5].

Maternal influenza vaccination plays a crucial role in protecting both mothers and infants. Vaccination of pregnant women not only reduces the risk of influenza and its complications for the mother but also confers passive immunity to the neonate through the transplacental transfer of influenza-specific antibodies. [5] These antibodies provide the neonate with some degree of protection against influenza during the first few months of life, a period when the infant is particularly vulnerable to infection. [6]

A growing body of evidence from clinical trials and observational studies supports the effectiveness of maternal influenza vaccination in reducing the risk of influenza in neonates. For instance, a study demonstrated that maternal influenza vaccination resulted in a significant reduction in the incidence of laboratory-confirmed influenza among infants aged less than six months [7]. Additionally, another study by found that maternal vaccination was associated with a decreased risk of severe influenza-related outcomes in infants, including hospitalization (France et al., 2006).

Maternal influenza vaccination has consistently demonstrated a significant reduction in the risk of influenza and other respiratory infections in neonates during their early months of life. Robust evidence from various study designs—including randomized controlled trials (RCTs), observational studies, and meta-analyses—strongly supports the efficacy of this preventive measure. Research shows that maternal immunization not only decreases the incidence of influenza in newborns but also mitigates the severity of the disease, thereby reducing hospitalization rates and overall health complications in this vulnerable population [9].

Randomized controlled trials, widely considered the gold standard for evaluating vaccine efficacy, have provided compelling data on the benefits of maternal influenza vaccination. For example, an RCT conducted in Nepal found that vaccination during pregnancy reduced the incidence of laboratory-confirmed influenza in neonates by 63% and resulted in a 29% reduction in influenza-like illnesses among infants [10]. Similarly, a study from South Africa reported a 50% reduction in influenza-associated hospitalizations in neonates, highlighting that maternal vaccination not only prevents influenza infections but also lessens disease severity and its associated healthcare burden [11].

Real-world evidence from observational studies further reinforces these findings. Large-scale investigations tracking diverse populations have consistently shown that maternal vaccination leads to a notable decrease in the occurrence of influenza-like illnesses in neonates, even in areas with high viral circulation. These studies underscore the protective role of transplacental antibody transfer, which provides infants with passive immunity during their most vulnerable period. Moreover, research reviewing health records across multiple regions has revealed that infants born to vaccinated mothers experience significantly lower rates of hospital admissions for respiratory infections in the first six months of life, directly attributing this improvement to the passive immunity conferred by maternal antibodies [12].

In addition to individual studies, systematic reviews and meta-analyses pooling data from numerous investigations have confirmed the effectiveness of maternal influenza vaccination. These comprehensive analyses have demonstrated a 40–60% reduction in neonatal influenza infections, underscoring the robust protective effect of antibodies transferred during pregnancy. Furthermore, these reviews highlight that maternal immunization is associated with reduced rates of preterm births and low birth weight, suggesting that by preventing influenza infections during pregnancy, the vaccine indirectly contributes to better neonatal outcomes. This is particularly significant given that preterm birth and low birth weight are critical factors in neonatal morbidity and mortality [13].

Despite the well-established benefits of maternal influenza vaccination, challenges remain in achieving high vaccination coverage. Barriers to vaccination include concerns about vaccine safety, lack of awareness among pregnant women and healthcare providers, and logistical issues such as vaccine availability. [8] Addressing these challenges through improved education, outreach, and healthcare infrastructure is essential to increasing

vaccination rates and maximizing the benefits of maternal vaccination for both mothers and infants.

Methods: Literature Search Strategy

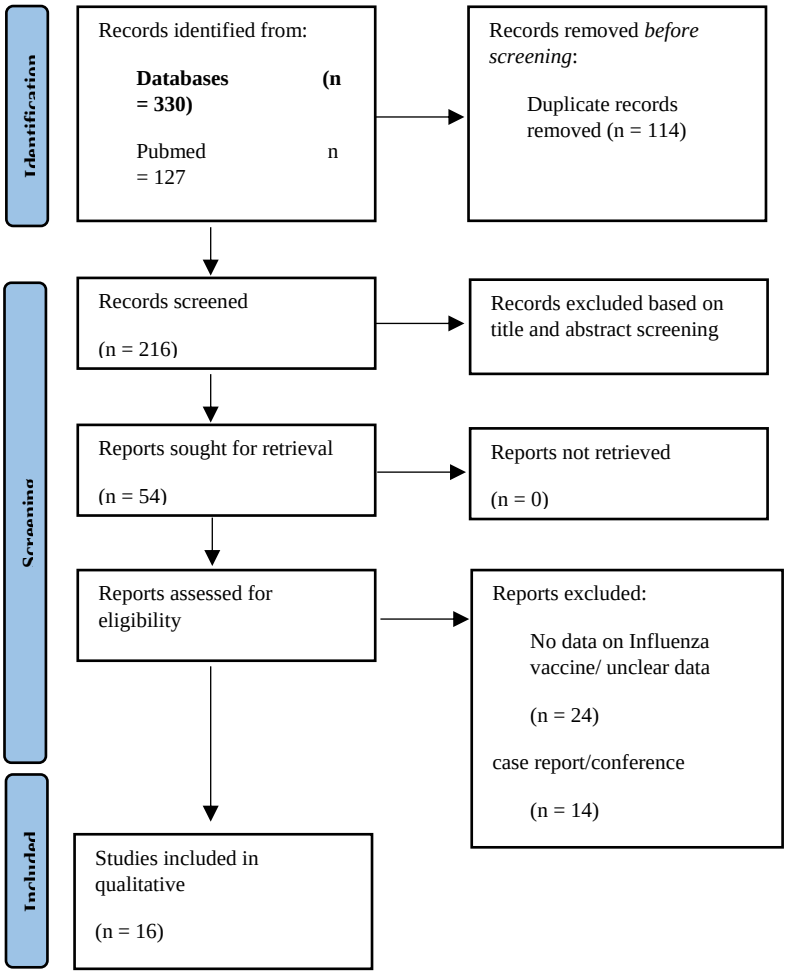
To ensure a comprehensive review, a systematic literature search was conducted across multiple databases, including PubMed, Scopus, and Web of Science. The following keywords were used: "maternal influenza vaccination," "neonatal respiratory infection," "passive immunity," and "vaccine effectiveness." Studies included were randomized controlled trials, observational studies, and meta-analyses published in peer-reviewed journals over the past two decades. Inclusion criteria were studies evaluating the impact of maternal influenza vaccination on neonatal health outcomes, while exclusion criteria included studies focusing solely on maternal health outcomes or lacking quantitative effectiveness measures.

Search result

The PRISMA flow diagram outlines the systematic approach used to identify and select studies for inclusion in this review on the effectiveness of maternal influenza vaccination in preventing neonatal respiratory infections. A comprehensive search across three major databases—PubMed, Scopus, and Web of Science—yielded 312 records, with an additional 18 identified from reference lists and grey literature, bringing the total to 330. After removing 114 duplicate records, 216 studies remained for screening. Titles and abstracts were reviewed for relevance, leading to the exclusion of 162 articles that did not meet the inclusion criteria. This initial screening ensured that only studies directly addressing maternal influenza vaccination and neonatal respiratory outcomes were considered further.

Following the title and abstract screening, 54 full-text articles were assessed for eligibility. Of these, 38 were excluded due to reasons such as focusing only on maternal outcomes, lacking quantitative effectiveness measures, or being of low methodological quality. Ultimately, 16 studies were deemed relevant and included in the final analysis. These studies provide robust evidence supporting the protective effects of maternal influenza vaccination in reducing neonatal respiratory infections. The structured selection process ensured that only high-quality, relevant studies contributed to the conclusions drawn, strengthening the reliability and validity of the review findings.

Figure 1: Summary of the studies selection and screening process



Mechanism of Protection: How Maternal Influenza Vaccination Safeguards Neonates Against Respiratory Diseases

Neonates are among the most vulnerable populations when it comes to influenza and other respiratory diseases due to their immature immune systems, which leave them defenseless against infections [13]. Unlike older children and adults, neonates are unable to generate strong immune responses to pathogens, making them highly dependent on maternal antibodies for protection in their early months of life. Since influenza vaccination is not recommended for infants under six months of age, maternal immunization serves as the primary strategy to protect neonates from influenza and its complications. This protection is primarily conferred through the transfer of maternal antibodies across the placenta and through breast milk, as well as by reducing the likelihood of maternal infection and transmission of influenza to the infant [14].

Below are some of the mechanisms of mechanism of protection

1. Passive Immunity Transfer

Maternal antibodies are transferred to the fetus through the placenta, primarily in the form of immunoglobulin G (IgG), which is the most abundant antibody subclass during pregnancy. These antibodies help protect the neonate from influenza infection during the critical early months of life, when the infant's immune system is still developing and unable to produce sufficient antibodies on its own [15].

Timing of Transfer:

The transfer of maternal antibodies to the fetus occurs primarily during the third trimester of pregnancy, with the peak of transfer in the last few weeks before delivery. This makes timely vaccination (ideally during the second or third trimester) crucial to ensure adequate levels of antibodies are transferred to the infant [4]. Vaccination during early pregnancy may not be as effective in transferring antibodies as vaccination later in the pregnancy.

Duration of Protection:

The antibodies transferred to the neonate typically provide protection for the first six months of life. This period coincides with the infant's highest vulnerability to severe respiratory infections, such as influenza. After six months, the level of passive immunity gradually declines, which is why infants are typically vaccinated against influenza starting at six months of age [10]. However, the passive immunity provided by maternal vaccination helps reduce the risk of influenza-related hospitalizations and death during the most vulnerable period of infancy.

2. Immune Response Dynamics

Maternal influenza vaccination does not only provide passive protection to the fetus but also induces a strong immune response in the mother. This immune response is key to ensuring that the mother remains protected from influenza during pregnancy and that sufficient levels of protective antibodies are available for transfer to the fetus [16].

Hemagglutination Inhibition (HAI) Antibodies:

One of the primary immune responses induced by influenza vaccination is the production of hemagglutination inhibition (HAI) antibodies. These antibodies are crucial for neutralizing the influenza virus by preventing it from binding to host cells. High titers of HAI antibodies in the mother correlate with a higher likelihood of robust antibody transfer to the fetus, thus providing the neonate with protective immunity [17].

Activation of Memory B Cells:

In addition to producing immediate antibodies in response to the vaccine, maternal influenza vaccination activates memory B cells. These cells are part of the adaptive immune response and play a crucial role in long-term immunity. Upon subsequent exposures to influenza virus or boosters, memory B cells can rapidly produce large amounts of antibodies.[9] This mechanism enhances the maternal immune response to future influenza infections and supports long-term protection for both the mother and her offspring [18].

3. Transplacental Transfer of Maternal Antibodies

The most significant mechanism by which maternal influenza vaccination protects neonates is the transplacental transfer of maternal immunoglobulin G (IgG) antibodies. These antibodies, generated in response to maternal vaccination, cross the placenta and enter the fetal circulation, providing the newborn with passive immunity against influenza during the first months of life [13].

IgG is the predominant antibody class involved in transplacental transfer and plays a key role in neutralizing viral pathogens, preventing viral attachment to host cells, and facilitating immune system recognition of infections. Among the different subclasses of IgG, IgG1 and IgG3 have the highest efficiency in crossing the placenta and are primarily responsible for neonatal protection against influenza and other respiratory infections [19].

The transfer of maternal antibodies begins early in pregnancy but reaches peak efficiency during the third trimester. This process occurs through Fc receptor-mediated transcytosis, where IgG antibodies bind to Fc receptors in the syncytiotrophoblast cells of the placenta and are actively transported into fetal circulation. By the time of birth, maternal antibodies provide neonates with robust immunity against influenza and other common respiratory viruses [20].

Studies have shown that maternal influenza vaccination administered during the second or third trimester results in significantly higher antibody titers in the newborn. Vaccination too early in pregnancy may not generate sufficient antibody

levels at the time of birth, while vaccination in the later stages ensures maximal transfer. Research indicates that IgG levels in neonates can exceed maternal levels by approximately 1.5 times due to active transport across the placenta [21].

While maternal antibodies provide protection against influenza in the neonatal period, this immunity is not permanent. The half-life of maternal IgG antibodies in the infant is approximately 21 days, meaning that their concentration declines gradually after birth. By around 5–6 months of age, maternal antibodies have largely waned, leaving the infant susceptible to influenza and other respiratory infections. This timeline explains why routine influenza vaccination is recommended for infants starting at six months of age—after passive immunity has declined and the infant's own immune system has matured enough to respond effectively to the vaccine [8].

4. Immune Priming and Enhanced Neonatal Immune Responses

Beyond direct passive immunity, maternal influenza vaccination may also play a role in priming the neonatal immune system to respond more effectively to infections after birth. This phenomenon, known as immune imprinting or programming, suggests that maternal antibodies can modulate the infant's immune development, leading to enhanced innate and adaptive immune responses [22,23].

Some studies indicate that neonates born to vaccinated mothers exhibit better immune recognition of influenza antigens, leading to more efficient viral clearance when they encounter influenza in their early months of life. This immune priming effect could be mediated by maternal antibodies influencing the development of B cells and T cells in the neonatal immune system [16,24,25].

In addition to preventing influenza infection, maternal antibodies may also reduce the severity of illness in neonates who do contract influenza. Infants with maternal antibodies tend to have lower viral loads, reduced inflammation, and a lower risk of complications such as pneumonia, bronchiolitis, and acute respiratory distress syndrome (ARDS) [24].

Barriers to Maternal Influenza Vaccination

Despite the well-documented benefits of maternal influenza vaccination, several barriers prevent pregnant women from receiving the vaccine. These barriers include vaccine hesitancy, accessibility issues, and challenges within health systems.

1. Vaccine Hesitancy

Pregnant women often exhibit hesitancy toward vaccination, which can result in low vaccination uptake. Key factors influencing this hesitancy include:

Concerns about Vaccine Safety for the Fetus: Many pregnant women are concerned about the potential risks of vaccination, particularly regarding the safety of the fetus. Despite evidence showing the safety of the influenza vaccine during pregnancy, such as the safety profile demonstrated in large cohort studies, fear and uncertainty about potential adverse effects remain a significant barrier to vaccination uptake [26].

Misinformation and Lack of Awareness about the Benefits of Vaccination: Pregnant women may not fully understand the benefits of influenza vaccination, especially in terms of protecting both the mother and neonate. Misleading information, especially from unverified online sources, can exacerbate these concerns. Research shows that a lack of knowledge about the effectiveness of maternal vaccination is a key reason for non-vaccination [7].

2. Accessibility Issues

Access to the influenza vaccine can be limited, particularly in certain geographic and socioeconomic contexts:

Limited Availability in Rural and Low-Resource Settings: Women in rural or low-resource settings may face challenges in accessing healthcare services, including maternal vaccination. Studies show that women in these areas are less likely to receive the vaccine due to logistical barriers, such as insufficient healthcare infrastructure and lack of availability at local health centers. This is particularly concerning in low- and middle-income countries where access to vaccines can be inconsistent [9].

Financial Constraints and Lack of Healthcare Infrastructure: The cost of vaccines and the lack of comprehensive maternal health services in low-income settings can further limit vaccination rates. In some countries, the influenza vaccine may not be covered by health insurance or may be too costly for women without adequate financial resources.5 This financial barrier disproportionately

affects marginalized populations and contributes to lower vaccination rates in these groups [12].

3. Health System Challenges

Several health system-related factors contribute to the challenges of improving maternal influenza vaccination rates:

Inadequate Training of Healthcare Providers to Address Vaccine Hesitancy: Healthcare providers play a crucial role in encouraging pregnant women to get vaccinated. However, many providers lack adequate training on how to address concerns and hesitancy regarding the influenza vaccine. A study found that a significant proportion of healthcare workers do not consistently discuss vaccination with pregnant patients, which may be due to a lack of confidence in handling vaccine hesitancy or concerns [17].

Weak Integration of Vaccination Programs into Antenatal Care: In many settings, maternal vaccination programs are not sufficiently integrated into routine antenatal care. This lack of integration can lead to missed opportunities for vaccination. Research indicates that improving the integration of vaccination into existing antenatal care frameworks significantly increases vaccination rates among pregnant women. Additionally, inconsistent vaccine recommendations and delivery across different healthcare systems may further undermine efforts to increase maternal vaccination uptake [5,27].

Strategies to Improve Maternal Vaccination Coverage

Increasing maternal influenza vaccination coverage requires a multifaceted approach that involves education, policy interventions, and strengthening global vaccination programs to improve access, knowledge, and vaccine uptake.

1. Education and Awareness Campaigns

Educational outreach programs are critical for reducing vaccine hesitancy and increasing awareness of the benefits of maternal vaccination.

Community Outreach: Community-based education programs are essential for raising awareness, especially in underserved areas. Studies have demonstrated that engaging community health workers and using culturally appropriate methods can significantly increase vaccination rates among pregnant women [18].

Healthcare Provider Training: Healthcare providers play a key role in encouraging maternal vaccination. Training providers to confidently address patient concerns has been shown to improve vaccination rates. For example, a study in the United States found that healthcare providers who were well-informed about vaccine safety and efficacy were more likely to recommend vaccination to pregnant women [18].

2. Policy Interventions

Policy interventions can help address structural barriers, such as cost and accessibility, to improve vaccine uptake.

Incentives: Offering financial and non-financial incentives has been shown to encourage vaccination. A study in the UK demonstrated that providing small incentives, such as transportation reimbursement, led to increased vaccination uptake among pregnant women. These incentives can reduce barriers to vaccination, such as financial constraints [22].

Integration into Routine Antenatal Care: Incorporating maternal influenza vaccination into routine prenatal care has proven to increase vaccine coverage. Research has shown that integrating vaccination services into regular prenatal visits ensures that vaccines are consistently offered, reducing missed opportunities [22].

3. Strengthening Global Programs

Global health programs and collaborations play a crucial role in improving maternal vaccination coverage, especially in low- and middle-income countries (LMICs).

Global Vaccine Action Plan (GVAP): The World Health Organization's Global Vaccine Action Plan (GVAP) outlines strategies for improving immunization coverage worldwide, with a focus on maternal immunization. GVAP encourages governments to prioritize maternal vaccination as part of broader public health efforts. This plan provides a framework for increasing vaccine access in all regions, including LMICs [5,28].

Partnerships with NGOs: Non-governmental organizations (NGOs), such as Gavi, the Vaccine Alliance, are vital in enhancing vaccine access in LMICs.

Implications for Neonatal Health

Maternal influenza vaccination not only protects the pregnant woman but also provides significant benefits to the neonate, particularly in terms of reducing morbidity and mortality

associated with influenza and improving long-term health outcomes.

1. Reduced Morbidity and Mortality

Maternal influenza vaccination has been shown to significantly reduce the incidence of severe respiratory infections and complications in neonates. Neonatal Hospitalizations Due to Respiratory Infections: Vaccinating pregnant women against influenza has been associated with a reduction in hospitalizations for respiratory infections in their infants. A study conducted in Nepal demonstrated a 63% reduction in laboratory-confirmed influenza cases among neonates whose mothers received the influenza vaccine during pregnancy. By preventing the transmission of the virus from mother to neonate, vaccination reduces the likelihood of severe illness requiring hospitalization [29].

Mortality Rates Associated with Severe Influenza in Neonates: The impact of maternal influenza vaccination extends to reducing neonatal mortality rates due to severe influenza. A meta-analysis of several studies found that maternal influenza vaccination significantly decreased the risk of influenza-related complications, including mortality, in neonates. This is especially important for vulnerable neonates with immature immune systems who are at higher risk for severe infections [30].

2. Long-Term Benefits

The benefits of maternal influenza vaccination extend beyond the immediate protection against influenza. These long-term effects can significantly improve neonatal health, particularly in terms of lung development and overall well-being. Improved Lung Health and Reduced Risk of Chronic Respiratory Diseases: Early exposure to influenza can have lasting effects on lung health. Maternal vaccination helps prevent the early-life exposure to the influenza virus, potentially reducing the risk of developing chronic respiratory diseases such as asthma or other pulmonary conditions [31]. Studies have shown that infants whose mothers were vaccinated against influenza had a lower risk of respiratory complications in the early months of life (Regan & Munoz, 2021).

Future Directions

As maternal influenza vaccination continues to evolve, several key areas of focus will help optimize its effectiveness, ensure broader coverage, and address gaps in access and acceptance. These areas include research into vaccine optimization, enhanced surveillance systems, and efforts to promote equity in vaccination.

1. Research on Vaccine Optimization

Ongoing research aims to enhance the effectiveness and safety of influenza vaccines for pregnant women, which could lead to improved neonatal health outcomes.

Adjuvanted Vaccines: One promising avenue is the development of adjuvanted vaccines. Adjuvants are substances added to vaccines to boost the immune response. Studies have shown that adjuvanted vaccines can be more effective in eliciting a strong immune response in pregnant women, who may have altered immune function [32]. Research is ongoing to determine the most suitable adjuvants that will improve protection without compromising safety, especially for vulnerable populations such as pregnant women.

Universal Influenza Vaccines: Another future direction is the development of a universal influenza vaccine that would provide protection against multiple influenza strains, including seasonal and pandemic variants. This type of vaccine would reduce the need for annual flu shots and provide more consistent protection for pregnant women and their neonates. Early-stage research shows promise for universal vaccines targeting conserved parts of the influenza virus [18]. Such vaccines could offer long-term protection against influenza, particularly in high-risk populations such as pregnant women and infants.

2. Surveillance and Data Collection

Effective surveillance and data collection are crucial for monitoring the impact of maternal influenza vaccination on both public health and neonatal outcomes.

Strengthening Global Surveillance Systems: Enhancing global surveillance systems is essential for tracking the impact of maternal influenza vaccination, especially in low- and middle-income countries (LMICs). Surveillance systems help identify trends in vaccine coverage, monitor the incidence of influenza, and assess the effectiveness of vaccines in real-world settings. For example, the Global Influenza Surveillance and Response System (GISRS), coordinated by the World Health Organization (WHO), plays a crucial role in global surveillance of influenza and monitoring vaccine effectiveness (WHO, 2020).

Strengthening such systems in LMICs will allow for better data-driven decision-making.

Conducting Longitudinal Studies on Long-Term Neonatal Health Outcomes: Long-term studies are needed to assess the sustained effects of maternal influenza vaccination on neonatal health. This includes monitoring neonatal lung function, the incidence of chronic respiratory diseases, and long-term immune health. Longitudinal studies would provide crucial data on whether the protective effects of maternal vaccination extend beyond infancy and reduce the incidence of respiratory diseases later in childhood [14].

3. Addressing Equity in Vaccination

Ensuring that maternal influenza vaccination is accessible to all populations, especially in resource-limited settings, is a crucial challenge that must be addressed.

Ensuring Vaccine Affordability and Accessibility in LMICs: Vaccine accessibility remains a significant barrier in many LMICs. Efforts must focus on making vaccines affordable and accessible to pregnant women in these regions. Organizations such as Gavi, the Vaccine Alliance, play a critical role in improving vaccine distribution and affordability in LMICs. Their support helps reduce financial and logistical barriers to vaccination in low-resource settings [20]. Continued support and investment are necessary to ensure that maternal influenza vaccines are widely available, even in the most underserved areas.

Addressing Sociocultural Barriers to Vaccine Acceptance: In addition to logistical challenges, sociocultural barriers also affect vaccine acceptance. Misinformation about vaccine safety, cultural beliefs, and mistrust in healthcare systems can lead to lower vaccination rates. Addressing these barriers requires targeted public health campaigns that engage local communities, educate individuals about vaccine safety, and build trust between healthcare providers and patients. Research has shown that culturally tailored interventions, which respect local beliefs and practices, can significantly increase vaccine acceptance in diverse populations [26].

Conclusion

Maternal influenza vaccination is a crucial preventive measure that provides neonates with passive immunity, protecting them from respiratory infections during their early months of life. The proven efficacy of this intervention in reducing neonatal morbidity and mortality underscores its importance. However, barriers such as vaccine hesitancy, misinformation, and limited access in low-resource settings continue to impede widespread adoption. Addressing these challenges through targeted education, better integration into antenatal care, and improved healthcare infrastructure is vital for increasing vaccination coverage.

Investing in maternal influenza vaccination is a cost-effective strategy that not only safeguards the health of mothers and their newborns but also yields long-term public health benefits. By enhancing global vaccination programs and ensuring equitable access, we can significantly improve neonatal health outcomes and reduce the burden of influenza-related diseases. Ultimately, strengthening maternal vaccination efforts offers a powerful tool to protect both maternal and neonatal health globally.

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