



## Review

# Influenza vaccine for pregnant women in resource-constrained countries: A review of the evidence to inform policy decisions

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## ABSTRACT

Seasonal influenza is responsible for three to five million severe cases of disease annually, and up to 500,000 deaths worldwide. Pregnant women and infants suffer disproportionately from severe outcomes of influenza. The excellent safety profile and reliable immunogenicity of inactivated influenza vaccine support WHO recommendations that pregnant women be vaccinated to decrease complications of influenza disease during pregnancy. Nevertheless, influenza vaccine is not routinely used in most low- and middle-income countries and is not widely used in pregnant women worldwide.

Two recent prospective, controlled trials of maternal influenza vaccination in Bangladesh and US Native American reservations demonstrated that inactivated influenza vaccine given to pregnant women can decrease laboratory-confirmed influenza virus infection in their newborn children. These studies support consideration of the feasibility of targeted influenza vaccine programs in resource-constrained countries.

Platforms exist for the delivery of influenza vaccine to pregnant women worldwide. Even in the least developed countries, an estimated 70% of women receive antenatal care, providing an opportunity for targeted influenza vaccination. Challenges to the introduction of maternal influenza vaccination in resource-constrained countries exist, including issues regarding vaccine formulation, availability, and cost. Nonetheless, maternal influenza vaccination remains an important and potentially cost-effective approach to decrease influenza morbidity in two high-risk groups – pregnant women and young infants.

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**Abbreviations:** ACIP, US Advisory Committee on Immunization Practices; ALRI, acute lower respiratory infections; EMEA, European Medicines Agency; FDA, US Food and Drug Administration; GACVS, WHO Global Advisory Committee on Vaccine Safety; HAI, serum hemagglutination inhibition (HAI) antibody; LAIV, live-attenuated influenza vaccines; MNT, Maternal Neonatal Tetanus; SAGE, WHO Strategic Advisory Group of Experts; TIV, trivalent inactivated influenza vaccine.

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## 1. Introduction

Every year, seasonal influenza causes three to five million severe cases of disease and about 250,000–500,000 deaths worldwide [1]. In high-resource countries, influenza vaccine is recommended annually, and priority is given to high risk groups including pregnant women, children, the elderly, and persons with chronic medical conditions [2]. Influenza prevention in infants remains problematic. Influenza vaccines are not licensed for children younger than 6 months, and antiviral chemoprophylaxis is not licensed for children younger than 1 year [2].

While influenza burden of disease data are limited from many resource-constrained countries, the risk of severe influenza outcomes among pregnant women and young children is likely to be higher than in developed country settings. Influenza vaccines are rarely used in resource-constrained countries for several reasons; including misperceptions that influenza is not a problem in such countries, vaccine cost, program implementation challenges, and logistical issues regarding vaccine availability, expiration dates, and optimal formulation.

The observation that maternal antibodies transmitted transplacentally confer protection against influenza during a newborn's first months of life suggests a potentially cost-effective and targeted strategy against maternal and neonatal influenza in resource-constrained settings [3–6]. Recently, two prospective, controlled vaccine trials conducted in resource-constrained settings demonstrated that laboratory-confirmed influenza virus infections are lower among young infants whose mothers received trivalent inactivated influenza vaccine (TIV) [7,8]. These new data, and the implication that two high-risk groups could be protected by vaccinating pregnant women, support an evidence-based analysis of benefits and challenges of influenza vaccine programs for pregnant women in resource-constrained settings.

In this article, we review the evidence on the immunogenicity, safety and impact of maternal influenza immunization for both mother and child, and we explore issues concerning distribution, logistics, and feasibility. The objective of this review is to inform policy decisions in resource-constrained countries, which includes identifying evidence gaps to help inform needed research. A systematic review was not feasible due to the limited clinical trial data in this area and due to the broad range of topics that factor into policy decisions.

## 2. Burden of influenza among pregnant women and newborn infants

### 2.1. Burden of influenza in pregnant women

Numerous studies have documented disproportionate rates of severe influenza infection among pregnant women during 20th century pandemics. During the 1918 influenza A (H1N1) pandemic, observations of increased morbidity and mortality among pregnant women were often documented [9,10]. During the 1957 influenza A (H2N2) pandemic, 50% of women of childbearing age who died were pregnant [11,12], and 10% of influenza deaths were among pregnant women [13].

Large epidemiologic studies within the last 20 years in high-resource countries have estimated population-based incidence rates of influenza-associated hospitalizations among pregnant women during interpandemic periods. When compared to non-pregnant women, pregnant women have increased odds of influenza-attributable hospitalizations [14,15]. In Canada, influenza-attributable hospitalizations accounted for 60% of all respiratory related hospital admissions among otherwise healthy pregnant women [15]. Odds of hospitalization for respiratory conditions increases by trimester (from OR 1.4 in second trimester to OR 4.7 in the third trimester), and otherwise healthy women in their third trimester have similar risks to non-pregnant women with chronic co-morbid conditions [14–19]. In addition, the presence of high-risk conditions such as asthma or diabetes increases the risk of influenza-associated hospitalization 3–10 times that of non-pregnant controls [14–16,18,20].

The morbidity of pregnant women was closely monitored during the 2009 influenza A (H1N1) pandemic, although most data came from temperate, developed countries [21]. In a South Africa case series, pregnancy or puerperium was the most common risk factor among all H1N1 deaths [22]. Similarly, a recent systematic review of 2009 pandemic influenza in pregnancy from predominantly high-resource countries found increased risks of hospitalization, ICU admission, and death [21]. Risk increases with gestational age [22–26]. In some studies, most hospitalized pregnant H1N1 cases were without underlying medical co-morbidities [24–30]. Others identified increased co-morbidities among severely ill pregnant women. For example, a study from South Africa found high rates of pulmonary tuberculosis (29%) and HIV (71%) among pregnant women who died with H1N1 influenza [22].

Adverse fetal influenza outcomes due to premature delivery or maternal demise have been reported for decades [31]. Population-based influenza studies are very difficult and expensive to conduct in this area, but many case reports of fetal and newborn complications from high-resource countries during interpandemic and pandemic influenza seasons exist [2,21,31,32]. During the 2009 influenza pandemic, fetuses and newborns of H1N1-infected women had an increased risk of poor clinical outcomes, primarily due to preterm birth rather than neonatal influenza [21]. Vertical transmission of H1N1 virus among pregnant women with influenza was uncommon [23,29], but it did occur [33]. Childbirth and neonatal outcomes were worse among infants born to H1N1-infected women [23,34]. An Australia/New Zealand case series of 60 deliveries to H1N1-infected women included complications of still birth (7%), infant death (5%), preterm birth (37%), and neonatal intensive care unit (ICU) admission (57%) [23]. Pregnant women with severe disease were more likely to deliver their babies during hospitalization for H1N1 virus infection [25], and 15–67% of severely ill women in their third trimester required emergent cesarean deliveries [23,27].

### 2.2. Burden of influenza in young children

In temperate regions, influenza has long been recognized as an important contributor to pediatric morbidity. Young infants have the highest rates of severe influenza compared to other pedi-

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