Strategies To Boost Maternal Immunization To Achieve Further Gains In Improved Maternal And Newborn Health

ABSTRACT Despite the indisputable successes of the United Nations Millennium Development Goals, which include goals on improving maternal health and reducing child mortality, millions of mothers and newborns still die tragically and unnecessarily each year. Many of these deaths result from vaccine-preventable diseases, since obstacles such as cost and accessibility have hampered efforts to deliver efficacious vaccines to those most in need. Additionally, many vaccines given to mothers and children under age five are not suitable for newborns, since their maturing immune systems do not respond optimally during the first few months of life. Maternal immunization—the process by which a pregnant woman’s immune system is fortified against a particular disease and the protection is then transferred to her unborn child—has emerged as a strategy to prevent many unnecessary maternal and newborn deaths. We review vaccines that are already used for maternal immunization, analyze vaccines under development that could be used for maternal immunization strategies in the future, and recommend that policy makers use maternal immunization for improved maternal and newborn health.

For the past fifteen years the United Nations (UN) Millennium Development Goals have shaped the world’s response to glaring inequalities in health. These eight international development goals were established following the UN Millennium Summit in September 2000. They focus on areas such as eradicating extreme poverty and hunger, improving education and environmental sustainability, and combating infectious diseases. Goals 4 and 5 focus on reducing child mortality and improving maternal health, respectively. Although impressive gains have been made in both of these areas, millions of mothers and children still die from preventable causes each year.

The mortality rate of children under age five decreased by more than half between 1990 and 2015, from ninety deaths to forty-three deaths per thousand live births, but that change did not meet the initial target of a two-thirds reduction in child mortality. In 2013 over 2.9 million newborns died, which represented 44 percent of all deaths of children under age five. As a consequence, achieving a reduction in neonatal mortality has remained a major focus of the global health agenda. Similarly, the global maternal mortality ratio (the number of maternal deaths per 100,000 live births) decreased by nearly half since 1990, but this fell far short of the goal of reducing the ratio by three-quarters. In 2013, 289,000 women died during pregnancy, childbirth, or the forty-two days following delivery.

In September 2015 the Sustainable Development Goals replaced the Millennium Development Goals as the UN strategy for combating
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Health inequalities. Maternal and child health again feature prominently in this global strategy to achieve health equality.

The leading causes of maternal and newborn deaths each year include hemorrhage, hypertension, unsafe abortion, and complications from preterm birth. However, vaccine-preventable diseases such as pertussis, tetanus, and influenza are also leading killers of mothers and newborns, despite the widespread distribution of vaccines throughout much of the world in recent decades. Increased uptake of vaccines for these diseases, particularly in low- and middle-income countries, could save the lives of thousands of mothers and children each year.

The World Health Organization (WHO), through its Global Vaccine Action Plan, has declared 2011–20 the Decade of Vaccines. The Global Vaccine Action Plan framework aims to extend immunization to everyone by ensuring that adequate resources are provided for vaccines, health systems, and supportive infrastructure and that more health workers are trained to reach remote and marginalized populations. The framework also advocates for the development of new vaccines and technologies to maximize the benefits of immunization around the world.

As the Decade of Vaccines passes its halfway point and the Sustainable Development Goals begin, maternal and newborn health must be kept at the forefront of global health policies, programming, and advocacy.

In this article we synthesize key information from the literature about vaccines that are being or have the potential to be used for maternal immunization. We use this information to provide policy recommendations for improving global maternal and newborn health.

We first examine the mechanism by which maternal immunization protects women and newborns, and we review maternal immunization for tetanus, influenza, and pertussis.

The Mechanism Of Maternal Immunization

Immunization during pregnancy can serve two vitally important purposes: It can provide protection against infectious disease to the mother and fetus during pregnancy, and it can pass this protection on to the newborn through infancy. This occurs through the placental transfer of antibodies, a natural phenomenon that occurs throughout gestation—primarily in the final four weeks of pregnancy—that results in protective antibody levels in the fetus sometimes reaching higher concentrations than those found in the mother.

Without this transfer of immune protection from the mother, newborns would be even more vulnerable to infectious diseases. Newborns have to adjust to the heterologous environment to cope with numerous external influences after birth. Newborns often do not respond well to vaccines and require multiple doses of vaccines spaced appropriately apart in time to prime their immune systems to deal effectively with a specific infection.

Conversely, a single dose can often immunize a pregnant woman who has already received a priming course of immunizations in her youth or has been exposed to the disease previously. Most vaccines are not used in newborns younger than six weeks. Therefore, maternal immunization, which has been shown to passively protect the baby for the first several months of life, can limit the amount of time a newborn lacks immune protection from numerous infectious diseases. Since most pregnant women routinely seek prenatal care, maternal immunization is not only a good medical option but also a feasible and cost-saving intervention for expectant mothers and their future newborns.

Vaccines Recommended For Use During Pregnancy

Tetanus Tetanus is caused by the spores of the bacterium Clostridium tetani, which exist in such abundant quantities in all soil and animal intestinal tracts that they contaminate numerous surfaces and substances and can never be fully eradicated. While tetanus can affect people of all ages, newborns and their mothers are particularly at high risk for infection if childbirth occurs under unhygienic conditions. Eliminating tetanus infections therefore requires immunization and high-quality health services that are universally accessible.

Over a million people died from tetanus each year in the 1980s, despite the fact that an effective vaccine, tetanus toxoid, had been available for decades. In 1988 the WHO estimated that 787,000 of the deaths that year were from neonatal tetanus, defined as tetanus in the first twenty-eight days of life. To decrease the impact of tetanus, in 1989 the forty-second World Health Assembly made a global commitment to eliminate neonatal tetanus—that is, to reduce its occurrence to fewer than one case per thousand live births in every country—by 1995. This commitment was updated in 1999 to include maternal tetanus and was renamed the Maternal and Neonatal Tetanus Elimination Initiative.

Annual neonatal tetanus deaths decreased to 490,000 in 1994 and to 200,000 in 2000 (Exhibit 1). The latest data, from 2013, show that 49,000 neonatal tetanus deaths still occur each
year.\textsuperscript{20} As of May 2015 maternal and neonatal tetanus had been eliminated in all but twenty-five countries, and overall deaths from tetanus had been reduced by 94 percent since 1988.\textsuperscript{21,22,23}

This reduction in tetanus deaths was achieved by reducing infection through the following four key strategies: the delivery of infants by skilled birth attendants to ensure clean delivery practices; maternal immunization with tetanus toxoid–containing vaccines; immunization of women of reproductive age in high-risk areas with tetanus toxoid–containing vaccines; and surveillance for neonatal tetanus.\textsuperscript{24}

Maintaining this decline in infections and ultimately eliminating deaths due to tetanus will require a sustained commitment from the international community. Maternal immunization has played a key role in the progress toward eliminating maternal and newborn tetanus thus far; continuing to use it as a strategy will be critical to saving at-risk maternal and newborn lives. It also provides a powerful example of the success of maternal immunization, which could be applicable to other vaccine-preventable infectious diseases.

\textbf{INFLUENZA} Pregnant women, new mothers, and newborns are also vulnerable to influenza infection, which can result in hospitalization; prematurity; stillbirth; and, in rare cases, death of the mother or newborn.\textsuperscript{25,26,27} Influenza vaccines given during pregnancy have been shown to produce an immune response that is passed on to the newborn\textsuperscript{28,29} and to reduce confirmed cases of influenza by up to 63 percent.\textsuperscript{30}

Because the risk of influenza infection is substantial for pregnant women, fetuses, and newborns, influenza immunization is recommended for all pregnant women at the beginning of the seasonal influenza epidemic, regardless of the stage of the pregnancy.\textsuperscript{31} Protecting newborns from influenza infection with maternal immunization is especially important, since influenza vaccination is not recommended for children younger than six months.\textsuperscript{32}

The effectiveness of maternal immunization, paired with epidemiological data showing that breast-feeding can protect against influenza infection in newborns,\textsuperscript{33} led the WHO to recommend in 2005 that all pregnant women be immunized against influenza.\textsuperscript{34} The US surgeon general recommended maternal immunization for influenza as far back as 1960,\textsuperscript{35} yet low rates of influenza immunization during pregnancy have persisted. A telephone survey found that in 2001–02 only 11.2 percent of pregnant women in the United States were vaccinated against influenza—a share that increased each year for three years but then plateaued for three years, reaching 26.9 percent in 2007–08 (Exhibit 2).\textsuperscript{36}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Exhibit1.png}
\caption{Estimated Number Of Deaths Worldwide Due To Neonatal Tetanus, 1980–2013, And Global Coverage With Tetanus Toxoid Vaccine, 1980–2014}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Exhibit2.png}
\caption{Influenza Immunization Rate Among Pregnant Women And Death Rate Of Children Under One Year Per 100,000 From Influenza And Pneumonia In The United States, 2001–13}
\end{figure}

\textbf{EXHIBIT 1}


The 2009 influenza A (H1N1) pandemic saw an upsurge in vaccine uptake, or coverage, and further increases have been seen since, resulting in a 52.2 percent coverage rate in 2013–14 and a decrease in the death rate from influenza and pneumonia over this period.\textsuperscript{37}

Given the seasonality of influenza that has been demonstrated in many resource-rich settings, it is now important to gather epidemiolog-
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Annual Number Of Pertussis Cases In The United States, 1922-2014

**EXHIBIT 3**

- **Source:** Authors' analysis of data from Centers for Disease Control and Prevention. Pertussis (whooping cough): pertussis cases by year (1922–2014) [Internet]. Atlanta (GA): CDC; [last updated 2015 Sep 8; cited 2015 Dec 17]. Available from: http://www.cdc.gov/pertussis/surveillance/cases-by-year.html.
pertussis organism from mother to baby.49

In 2008 an estimated sixteen million cases of pertussis and 195,000 deaths from pertussis occurred in children worldwide, making the size and scale of the recent outbreaks in the United States and United Kingdom pale in comparison.50 Deaths in settings where maternal vaccination programs have been introduced have dropped dramatically. Of the thirteen reported pertussis deaths in the United States in 2014, eight occurred in infants under three months.51 Higher rates of maternal immunization worldwide could dramatically decrease the number of cases and deaths from pertussis.

The Safety Of Maternal Immunization

Maternal immunization has been used as a strategy to protect mothers and newborns for decades,52-57 and numerous studies have confirmed the safety of vaccines for this purpose.52-57

Despite overwhelming data supporting the safety of these vaccines, many pregnant women, because of fears about safety, still refuse to accept maternal immunization as a preventive strategy against infectious disease. Other reasons for refusing immunization include a perceived low risk of exposure to particular diseases and a lack of trust in the information about the vaccine.58 The lack of encouragement for or knowledge about maternal immunization by health care workers and the lack of infrastructure to store and distribute vaccines, particularly in low-resource settings, also contribute to poor uptake of maternal immunization.

This evidence suggests that a more comprehensive strategy is required to eliminate misinformation about immunization safety and efficacy in pregnancy, train health care workers about the benefits of maternal immunization, and develop the infrastructure required to implement maternal immunization worldwide.

High-level policy documents such as the WHO’s Global Vaccine Safety Blueprint are helpful in promoting top-down approaches to reassuring the public about vaccine safety.59 However, more must be done from the bottom up to translate policy into action.

The Future Of Maternal Immunization

A number of other vaccines have been used safely and effectively in adults and children for many years and should be tested for use in pregnant women, including vaccines against pneumococcus, *Haemophilus influenzae* type b, and meningococcus.59 Uptake of these vaccines in areas where these types of infections are endemic could be strategically advantageous. Clinical trials for the use of the twenty-three-valent pneumococcal vaccines during pregnancy have been completed, although results thus far have been inconclusive.59 Continuing to test these vaccines for safety and efficacy should remain a priority.

There are also several new vaccines in the pipeline that have the potential to be used for maternal immunization. A vaccine against group B Streptococcus, the most common cause of bacterial sepsis and meningitis in newborns in high-income countries and a common cause in low- and middle-income countries, could be used to prevent infection in newborns when given to pregnant women.59 Safety and immunogenicity data are already available from field trials, but more studies are needed to evaluate the effectiveness of the vaccines.60-63

Similarly, vaccines under development for respiratory syncytial virus,64 herpes simplex virus,65,66 and cytomegalovirus67 could be transformative for worldwide maternal and child health, if proven to be safe and effective for pregnant mothers and their offspring. Maintaining momentum in developing these vaccines will be essential to their successful approval, as it can often take more than ten years to develop a fully licensed vaccine, with costs of $200-$500 million.68

A continued focus on preventing these types of infections should remain a high priority as the Sustainable Development Goals gain momentum. To further support the prioritization of maternal and newborn health, we propose that policy makers consider the following recommendations when developing national and global strategies for saving the lives of women and children.
Policy Recommendations

The Millennium Development Goals have led to decreases in deaths of mothers and children worldwide, yet too few countries have reached the specified targets of goals 4 and 5. Since a significant proportion of these deaths are preventable, policy makers should continue prioritizing the lives of vulnerable mothers and infants in particular. Global frameworks such as the WHO’s Strategies Toward Ending Preventable Maternal Mortality and Every Newborn: action plan recommend human rights–based strategies and set specific targets for reducing national maternal mortality ratios and ending preventable newborn deaths and stillbirths. Focusing on essential care during labor, birth, and the first day and week of life and integrating maternal and newborn care are two strategies that could have significant impacts.

In addition, vaccines against tetanus, influenza, and pertussis have been proven to be safe and effective in preventing infections in mothers and newborns, particularly in high-income countries such as the United States and the United Kingdom. Providing these vaccines to pregnant women in low- and middle-income countries should be a priority. The strategy set out by the Global Vaccine Action Plan should be updated to emphasize the importance of maternal immunization and set specific targets for immunization coverage rates in areas where tetanus, influenza, and pertussis infection are endemic.

Vaccines and other drugs often face excessive hurdles on the path from research to market. When proven to be safe and effective, vaccines that are given accelerated approval and market protection could be transformative in saving the lives of women and newborns in maternal immunization programs. Innovative strategies that could be implemented to expedite development and increase uptake include developing public-private partnerships for research and development, committing to advance contracts, patent buyouts or extensions, and tax credits for vaccine sales.

A number of vaccine candidates exist that could be useful for maternal immunization. Priority should be given to vaccines against diseases that weigh considerably in the global burden of disease and where the potential benefits are high. Accompanying research and ongoing surveillance should be supported. However, increasing overall funding for research and development is only the first step toward increased uptake. Innovative strategies such as diversifying sources of funding for new vaccines, advocating that governments invest in immunization at incremental levels according to their ability to pay, and using differential pricing approaches to pay for available vaccines are all potential pathways to increased development and uptake of maternal immunization.

Conclusion

Maternal immunization has proved to be a safe and effective strategy for preventing specific infections for many years and has saved many lives of mothers and newborns. The disease burden of tetanus, influenza, and pertussis has been minimized in many countries through maternal immunization, but wider applications of this strategy are now needed. Millions of mothers and newborns still die each year from infectious diseases, particularly in low- and middle-income countries where vaccines are not as widely distributed or recommended in maternal immunization programs, or where access to prenatal care is quite difficult to achieve. In addition, a number of other vaccines in the pipeline could be used in pregnant women, provided they are found to be safe and effective. As the second half of the Decade of Vaccines begins and usheres in the Sustainable Development Goals, maintaining a long-term focus on saving the lives of the most vulnerable should be the primary focus of the global health community. Maternal immunization should be a cornerstone of this strategy.

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