Maternal immunization: trends in South and Southeast Asian countries

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ABSTRACT
Maternal immunization has the potential to reduce neonatal deaths caused by vaccine-preventable infectious diseases. Elimination of maternal and neonatal tetanus from many countries illustrates the potential benefits of maternal immunization as a strategy to decrease neonatal mortality caused by vaccine-preventable infections. Many countries in South and Southeast Asia have high cases of neonatal deaths, which were historically attributed to vaccine-preventable infections. Still, these countries vary in recommendations regarding immunization of pregnant women. We reviewed the current recommendations for the use of tetanus toxoid, tetanus–diphtheria, or tetanus–diphtheria–acellular pertussis (Tdap) vaccines for immunization of pregnant women. In addition to protection against tetanus and diphtheria, administration of the Tdap vaccine to pregnant women could help protect neonates against pertussis until they can receive the first two vaccine doses of their primary course. Vaccination against seasonal influenza is also recommended in many countries worldwide for pregnant women as influenza can pose health risks for the mother–fetus unit and the infant. Despite the recognized benefit of influenza vaccination for pregnant women, only some South and Southeast Asian countries have implemented its recommendation. The success of maternal tetanus vaccination has kindled the interest in vaccines that can be safely administered during pregnancy. Future availability of vaccines against respiratory syncytial virus and group B streptococcus, for use in pregnant women, could help prevent neonatal infections, especially in regions where diseases are less controlled. Communicating the body of evidence that supports maternal immunization to obstetricians is key for achieving optimal vaccination coverage to ensure protection of neonates. The current review aims to create awareness about the existing and potential benefits of maternal immunization in South and Southeast Asia.

Introduction
In 2018, 2.5 million children died before reaching the age of one month [1]. Based on 2012 estimates, approximately 36% of neonatal deaths would be caused by preterm birth complications, 23% by intrapartum conditions, and 23% by infections [2]. Neonates and young infants can however be protected against some early infections by antibodies inherited from their mothers [3,4]. When antibody concentration is sufficiently high, during the second and third trimesters of pregnancy, transplacental transfer can provide maternal immunity to newborns for their initial months of life [5]. Vaccination of pregnant women, often referred to as maternal immunization, aims at ensuring that sufficiently high concentration of immunoglobulin G (IgG) are available for transfer in utero to the fetus [3–5]. Transplacental transfer is influenced by several factors such as IgG concentration and subtype, though the full mechanism of transfer is yet to be elucidated [3,5].

Maternal antibodies typically wane over six months, providing protection until infants receive their own primary vaccinations [5,6]. Aside from the maternal IgG transferred through the placenta, maternal IgA antibodies excreted in the colostrum and breast milk can pass on to breastfeeding babies, potentially adding to the protective effects of maternal immunization [4,5,7].

Annual neonatal mortality is high in countries from South and Southeast Asia [1]. Furthermore, these regions historically have high cases of severe infections including tetanus and pneumonia [8–10]. The
disparity between countries from South and Southeast Asia with regards to neonate and infant health, and the gaps in recent national data make it difficult to assess the need for vaccination during pregnancy in these regions. Moreover, recommendations about maternal vaccination vary between countries and are sometimes complemented by recommendations from physician associations. Based on a search of the peer-reviewed literature (Supplementary Material 1), we review the trends in neonatal vaccine-preventable deaths and existing maternal immunization programs in South and Southeast Asian countries.

**Neonatal deaths in South and Southeast Asia**

India, Pakistan, Indonesia, Bangladesh, and the Philippines have the largest birth cohorts in the South and Southeast regions, with more than two million births in 2019 (Figure 1) [11,12].

Infections and perinatal health are known to contribute to the high neonatal mortality rates observed in the South and Southeast Asian regions [1]. In 2019, approximately 22% (522,000 deaths) and 10% (248,000) of the 2.4 million neonatal deaths that occurred worldwide, were reported in India and in Pakistan, respectively [1]. In South and Southeast Asia, most of the countries have high (>10.0/1000) neonatal mortality rates, with the highest estimated in Pakistan (41.2/1000 live births), Myanmar (22.45/1000), Lao People’s Democratic Republic (21.96/1000), India (21.66/1000), and Nepal (19.78/1000) [1].

Infections are known to contribute to neonatal deaths, though their nature and relative proportions vary across countries according to specific gaps in the healthcare systems and disease controls [2]. A prospective cohort study conducted in South Asia and sub-Saharan Africa evidenced that severe neonatal infections was the second leading cause of neonatal
deaths (35%) in South Asia [13]. This observation is in agreement with the results from a community surveillance conducted in Bangladesh where infections (29.3%) were found to be the leading cause of death after birth asphyxia (43%) [14]. In India, where the neonatal mortality rate was shown to vary widely across states, neonatal sepsis/infections accounted for 6.1% of neonatal deaths [15]. Unfortunately, it is difficult to properly assess incidence of vaccine preventable disease in neonates and related mortality as these data are scarce in the South and Southeast Asian regions. Indeed, surveillance programs, when in place, mainly monitor neonatal tetanus.

Trends in tetanus, diphtheria, and pertussis vaccination during pregnancy in South and Southeast Asia

Maternal and neonatal tetanus elimination

Perinatal tetanus caused a tremendous burden to mothers and neonates until its elimination in most of the South and Southeast Asian countries [16–24]. Neonatal tetanus and associated deaths were underreported and neglected until the 1980s. By then, community-based surveys, as conducted in India, provided estimates of neonatal tetanus mortality rate up to 60 per 1000 live births, accounting for 23–72% of all neonatal deaths [25]. The recommendation of maternal tetanus vaccination in 1983 led to a sharp decrease in tetanus neonatal deaths in India [26], though sociodemographic diversity and rurality posed challenges in some of the states [25]. In 2015, India was declared free of maternal and neonatal tetanus by the World Health Organization (WHO) [26]. Maternal immunization is included in the recommended WHO strategies to eliminate maternal and neonatal tetanus, along with the promotion of clean deliveries and adequate umbilical cord care practices [27].

Since the 1980s, when maternal tetanus toxoid (TT) vaccination was introduced in many countries as part of the maternal and neonatal tetanus elimination program, great efforts have been made to improve tetanus vaccination among pregnant women [28]. In 2019, WHO coverage estimates for maternal tetanus vaccination were still under 80% for Nepal, Pakistan, the Philippines, Brunei, Cambodia, Indonesia, and Laos (Table 1). Nevertheless, Cambodia, Indonesia, and Philippines made great strides in promoting maternal health, by increasing the proportion of delivery assisted by a skilled birth attendant from 32% to 89%, from 66% to 94%, and from 58% to 84%, respectively, over the 2000–2018 period [28]. Although Pakistan has partially eliminated maternal and neonatal tetanus (Punjab province) by 2018 [30,31], it remains the sole country of the Southern and Southeastern region of Asia where maternal and neonatal tetanus is present [28,32].

Maternal Td vaccination

While TT vaccines helped eliminate neonatal tetanus, WHO recommended in 2017 to replace TT vaccines with tetanus–diphtheria (Td) vaccines in order to sustain protection against diphtheria along with tetanus [33]. The rationale for this recommendation is based on observation of diphtheria immunity waning after the primary diphtheria–tetanus–pertussis (DTP) vaccination during the first year of life. Indeed, the most recent outbreaks of diphtheria are thought to have arisen where coverage of diphtheria-containing booster vaccines was low, as suspected for the 2017 outbreak in Indonesia where outbreaks are thought to be associated with immunity gaps in some areas [34]. For example, India, Nepal, and Indonesia have reported 96–99% of the diphtheria cases in Southeast Asia between 2000 and 2017 [35]. Moving from TT to Td and eventually to tetanus–diphtheria–acellular pertussis (Tdap) vaccines for maternal and neonatal tetanus elimination could help control diphtheria and provide additional protection against pertussis to infants during their first months of life [35,36].

Maternal Tdap vaccination

Pertussis, also referred to as whooping cough, is a highly contagious disease that affects the respiratory tract. The disease is still endemic worldwide and can
have severe complications in young infants [36]. Review of epidemiological data on neonatal pertussis published between 2000 and 2018 has shown that the burden of neonatal pertussis and related complications is high in South and Southeast Asia [37]. The number of pertussis cases observed per year has increased in infants younger than three months old. Indeed, infant mortality rates due to pertussis ranges between 5.6% and 14.7% in the region [37]. In India, review of 36 pertussis cases admitted to the pediatric intensive care unit showed that 27.7% of those infected were infants below six weeks of age, the youngest age to receive the first dose of the tetanus–diptheria–pertussis vaccine [36,38].

While the number of pertussis cases decreased following inception of the Expanded Program on Immunization by the WHO in 1974 and the subsequent launch of the Universal Immunization Program in 1985, the disease is recently reemerging in India (from about 31,000 total cases reported in 2005 to about 37,000 in 2016) and might well be underreported due to passive surveillance system [39]. Further review of the epidemiological data over the 2000–2017 period has confirmed this trend for the Southeast Asian region [40]. However, improved surveillance and more sensitive diagnostic tools might contribute to the higher observed incidence of pertussis observed in some countries (India, Laos, Malaysia, and Singapore) [39,40]. Nevertheless, national and regional surveillance systems are needed to assess the true burden of pertussis within the countries and by age groups.

Vaccination of pregnant women could be an effective way of protecting children against such infectious disease during their first months of life (i.e. until they receive their primary vaccination) [36,41–43]. Several strategies have already been adopted in other countries as a measure to reduce the burden of pertussis in neonates and young infants. In particular, more than 40 countries worldwide have recommendations for Tdap during pregnancy, including advanced countries like the United States, the United Kingdom, and Australia [11,44]. In these countries, the strategy was assessed as cost-effective [45–47]. However, such data are lacking for the South and Southeast Asian regions. It is noteworthy that in Australia, the United States, the United Kingdom, and Spain, maternal immunization during the second and third trimesters showed effectiveness ranging between 69% and 91% in reducing pertussis incidence in infants too young to be vaccinated [48–51].

Several studies have demonstrated that Tdap vaccination during pregnancy causes no harm to the fetus or mother [44,52–54]. Results from a clinical trial with 370 Thai women aged 18–40 years who received Tdap vaccination at 26–36 weeks of pregnancy showed that the vaccine has an acceptable safety profile; mild pain and low grade fever being the most common reported adverse events [53]. Concentrations of antibodies against pertussis toxin, filamentous hemagglutinin and pertactin were high in maternal as well as umbilical cord blood samples [53]. In Vietnam, comparison between 51 pregnant women vaccinated with Tdap and 48 vaccinated with TT evidenced that both vaccines had comparable safety profiles. Most common adverse events were stiffness, swelling, and itching at injection site (44% of women in Tdap vs. 43% in TT group) [52]. Pregnant women who received Tdap vaccination during pregnancy had higher concentrations of all measured antibodies, i.e. IgG against tetanus, diphtheria, and pertussis antigens (pertussis toxin, filamentous hemagglutinin, and pertactin), at delivery [52]. Relatively high amounts of anti-tetanus antibodies were detected in the umbilical cord blood in both vaccine groups and waning of maternal immunity occurred within the two first months of life.

Despite the potential benefit of maternal immunization against pertussis and the WHO recommendation to consider the vaccination of pregnant women with one dose of Tdap, most of the South and Southeast Asian countries continue to recommend TT vaccine for pregnant women or women of childbearing age (Table 2). Singapore is the only country within the region that has introduced the recommendation of vaccinating pregnant women between 16 and 32 weeks of gestation into its health program since 2017.

### Table 2. Maternal immunization programs in South and Southeast Asian countries [11].

| Vaccine | Countries |
|---------|-----------|
| TT      | Brunei, Cambodia, Malaysia, Nepal, Pakistan*, Sri Lanka, Vietnam |
| Td      | Bangladesh*, Bhutan, India, Indonesia*, Laos, Myanmar, Nepal, Philippines, Thailand |
| Tdap    | Singapore |
| Flu     | Brunei, Bhutan, Laos, Malaysia, Myanmar, Singapore, Thailand |

Flu: influenza vaccine; Td: tetanus–diphtheria vaccine; Tdap: tetanus–diphtheria–acellular pertussis vaccine; TT: tetanus toxoid vaccine.

*Childbearing age women and pregnant women.

*Given to all 15 years old women.
However, some associations of physicians have edited their recommendations regarding vaccination during pregnancy accordingly. For example, in India, the Federation of Obstetric and Gynecological Societies of India (FOGSI) recommends the Tdap and influenza vaccinations for pregnant women since 2016 [55]. The Philippine Foundation for Vaccination recommends the use of Tdap for pregnant women since 2015 [56]. The Infectious Disease Association of Thailand recommends Tdap vaccination for pregnant women since 2018 [57]. All these recommendations have the potential to supplant the national immunization program, although the impact is difficult to evaluate.

Maternal influenza vaccination

As per WHO, pregnant women should be included in influenza vaccination programs together with other risk groups, i.e. children aged 6 months to 5 years old, the elderly, individuals with chronic medical conditions, and healthcare workers [58]. The absence of national recommendation for influenza vaccination during pregnancy in more than half the South and Southeast Asian countries (Table 2) is surprising in light of the risks encountered by the fetus and mother in case of infection, particularly in case of pandemic influenza [59]. A systematic review of Indian studies suggested that influenza mortality was higher and that disease episodes were more severe in pregnant women than in non-pregnant population [60]. Birth outcomes were also found to be potentially impacted by influenza infection during pregnancy, with fetal mortality ranging from 5.5% to 33% and prematurity rates from 20% to 33% [60]. A retrospective study conducted in a tertiary care center in Rajasthan led to the conclusion that mortality was significantly higher in pregnant women infected with 2009 influenza A H1N1 pandemic (A/H1N1pdm09) than in other infected women (36% vs. 17%) [61]. This is further supported by data from a retrospective analysis of 6203 A/H1N1pdm09 cases from Rajasthan, as pregnancy was found to be the predominant predisposing factor [62]. A similar retrospective analysis of data from Singapore also found an increased risk of hospitalization in pregnant women infected with influenza A/H1N1 when compared with non-pregnant women of childbearing age (relative risk 26.3; 95% confidence interval (CI): 20.1–34.6) [63].

In India, influenza vaccination of pregnant women is recommended by FOGSI, though uptake was observed to be low for pandemic and seasonal influenza vaccines in the pregnant population [60]. Reported uptakes of influenza vaccination during pregnancy ranged between 0.0% and 12.8% [64–66]. Vaccinated mothers and their newborn children from Hyderabad (Southern India) were found to be protected against seasonal influenza without significant maternal adverse effects, as numbers of symptom-free pregnant women and new-borns were consistently higher in the vaccinated group when compared to the unvaccinated one [67]. However, a questionnaire-based study conducted in Srinagar (Northern India) between October 2012 and April 2013 evidenced that none of the 1000 pregnant women surveyed had been offered or received influenza vaccine [64].

In Thailand, where vaccination is recommended during the second and third trimesters of pregnancy, the frequency of adverse events following administration of influenza vaccine in pregnant women was found similar to those typically reported in healthy adults [68]. However, despite the national recommendation to vaccinate pregnant women, a cross-sectional survey revealed that only 25% of Thai physicians working at antenatal care clinics routinely recommended influenza vaccination in 2013 [69]. Nevertheless, a cross-sectional survey of 627 Thai pregnant women aware of influenza vaccination showed that 42% were willing to get the vaccine, suggesting that their attitude toward vaccination and their perception of associated benefits were good [70].

Similar to Tdap vaccination, cost-effectiveness data of influenza vaccination in pregnant women are lacking for South and Southeast Asian countries, though for high-income countries such as the US and Japan, maternal influenza vaccination is assessed as a cost-effective strategy [71,72].

Other available and future vaccines for maternal immunization

Vaccines against other diseases such as hepatitis A and B, or pneumococcal and meningococcal diseases may be administered to pregnant women in specific circumstances, i.e. when the risk of infection outweighs the potential risk of vaccination [5,73].

Moreover, proven benefits of maternal immunization against tetanus, influenza, and pertussis have reignited the interest of health professionals to develop new strategies against infections that threaten infants during their first months of life [3,4]. Other vaccines such as group B streptococcus (GBS) and respiratory syncytial virus (RSV) are anticipated to
be impactful for neonatal health, should they become available for vaccination of pregnant women [74].

Despite the paucity of data about RSV-related mortality and morbidity in Southeast Asian countries, RSV is known to account for a major fraction of reported acute respiratory tract infections [75]. In India, for example, 24.5% of less than five years of age children hospitalized for acute respiratory tract infections were positive for RSV, among whom 90% were younger than 2 years of age [76].

GBS also poses an important health burden to infants, being one of the leading causes of neonatal sepsis and meningitis [77]. Results from a modeling approach estimated that in 2015, Asia had the highest number of early-onset cases (95,000), of which 42,500 occurred in South Asia and 19,400 in Southeast Asia [78]. Very few countries in the world offer universal screening for GBS during the 36th week of pregnancy. In a country like India, where screening measures are not followed, GBS vaccination to pregnant women could help alleviate neonatal mortality due to the disease.

**Barriers to maternal immunization**

Key barriers include safety concerns, questions about the need for vaccination, efficacy of vaccines, lack of recommendation from healthcare workers, and lack of access to healthcare services [79]. Healthcare worker recommendation is known to be an important factor in vaccine confidence and uptake [80]. A publication from Singapore among local obstetricians evidenced that, despite their good knowledge of the safety, effectiveness, and benefits of Tdap and influenza vaccination in pregnant women, there was a gap in their knowledge regarding Tdap recommendations in local guidelines [81]. Moreover, aside from the limited knowledge of local obstetricians about vaccine recommendations, lack of time to inform patients was assessed as the main barrier to maternal vaccination [81].

However, other important factors are to be taken into consideration when assessing barriers to maternal immunization. The lack of official maternal immunization programs and associated reimbursement, as well as weaknesses in the health system due to inadequate financial and human resources are major impediment to antenatal vaccination [82].

**Conclusions**

Infections cause a high burden to neonates and contribute to neonatal deaths in South and Southeast Asia. However, vaccination of pregnant women is geared to protect newborn babies and vulnerable pregnant women. In South and Southeast Asian countries where recommendations are in place, Tdap and influenza vaccination of pregnant women is thought
to alleviate the burden caused by tetanus, diphtheria, pertussis, and influenza to mothers and neonates. However, full assessment of the impact of maternal immunization programs in place in the South and Southeast Asian regions is difficult due to gaps in coverage and cost-effectiveness data. Other vaccines under development for maternal immunization may help to control other diseases such as RSV and GBS.

Local obstetricians are key vaccinators as their recommendations are targeted to the future mother, taking into account the risk and benefits for her and her offspring. It is important therefore to establish continuous open communication on the body of evidence that build confidence on maternal vaccination strategy and to address programmatic barriers that countries in the South and Southeast Asian region are facing. Figure 2 summarizes the context, outcomes, and impact of this review for healthcare professionals.

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Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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