

REVIEW



Key considerations for successful implementation of maternal immunization programs in low and middle income countries

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ABSTRACT

The Maternal Neonatal Tetanus Elimination program is proof of concept for the feasibility and potential for maternal immunization to reduce neonatal mortality particularly in low and middle-income countries. Introduction of any additional vaccine into the antenatal space, such as Influenza and Pertussis, and potentially Respiratory Syncytial Virus and Group B Streptococcus vaccines in the future, requires strengthening of antenatal care and immunization services. Successful implementation also requires robust disease surveillance in pregnant women and neonates and active surveillance for adverse events following immunization to monitor the impact and ensure the safe use of the vaccine. This review outlines five key elements essential for successful implementation of a maternal immunization program focusing particularly on low and middle-income countries. These include; relevant considerations in supporting a decision to undertake a maternal immunization program including knowledge of local disease epidemiology, involvement of the consumer, healthcare provider recommendation, equitable access to maternal vaccination, and systems for disease surveillance, program evaluation and safety monitoring.

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Introduction

Vaccination during pregnancy (maternal immunization) is a promising strategy for reducing neonatal mortality from infectious diseases. With an expanding repertoire of maternal vaccines currently recommended^{1–3} or in development,⁴ international, national and regional health policy makers must increasingly make decisions about implementing vaccines outside the infant immunization schedule. These often require different service delivery approaches to reach pregnant women. The World Health Organization (WHO) provides guidance for national immunization program managers and policy-makers to support the introduction of new vaccines.⁵ Specifically, in relation to immunization of pregnant women, a regional field guide and a global maternal influenza vaccine introduction manual suggest that data on disease burden, and vaccine efficacy and safety be considered in order to inform prioritization of health interventions and operational plans for delivering influenza vaccines to pregnant women.^{6,7}

Nearly half of global under-five mortality occurs in neonates (infants in the first 28 days of life)^{8,9} and 86% of neonatal deaths occur in low and middle income countries (LMICs).^{8,10} Infectious diseases, particularly pneumonia, respiratory illness and sepsis, account for approximately 23% of neonatal deaths globally.¹¹ Relevant to maternal immunization is the Sustainable Development Goal to end preventable deaths of newborns.¹⁰ While childhood vaccination programs have had a significant impact on reducing mortality in the under-five age group, they have been less successful in reducing deaths in neonates given that most vaccines can only be administered from six weeks of

age, and full immunity often requires more than one dose. Therefore, neonates and very young infants are particularly vulnerable to vaccine-preventable infections, and due to their physiological immaturity suffer disproportionately from the complications of these infections.^{12,13}

Maternal immunization is a promising strategy to reduce infection in neonates and infants, particularly in LMICs where the burden of vaccine-preventable diseases is the greatest.¹⁴ Maternal immunization results in transfer of maternal antibodies across the placenta and through breastmilk to provide short-term passive immunity to the infant.^{15–17} Three vaccines (tetanus, influenza, and pertussis) are routinely recommended during pregnancy in different settings, although only tetanus has been implemented globally. In addition, new vaccine candidates against Respiratory Syncytial Virus (RSV) and Group B Streptococcus (GBS) are currently in development or clinical trials. If demonstrated to be effective and safe, these hold great potential to impact on two diseases that contribute significantly to neonatal morbidity and mortality.

Gavi, the Vaccine Alliance, is an international organisation that was created to improve access to new and underused vaccines for children living in the world's poorest countries.¹⁸ In line with the Sustainable Development Goals, Gavi supports these initiatives with financial support for vaccines that have demonstrated a direct benefit to the health of pregnant women and children. Every five years, Gavi takes stock of available and expected vaccines to develop a new vaccine investment strategy and to set new priorities for its vaccine support program through in-depth analysis and extensive consultations.^{19,20} For each

vaccine, Gavi identifies and reviews the latest evidence against a set of evaluation criteria and in the final phase of its evaluation provides recommendations for new vaccine investments.¹⁹ In 2018, two vaccines targeting pregnant women (RSV and influenza), were considered by the Gavi board.²⁰ RSV vaccine was considered as a candidate for endemic disease prevention and the landscape of interventions regarding pandemic influenza preparedness were assessed.

Given the rapidly expanding literature on maternal immunization, and recent publications attempting to close the gaps in knowledge required to inform policy on currently recommended or upcoming vaccines, this review synthesises and summarises some of the key elements for successful implementation of maternal immunization particularly focusing on low and middle-income settings, acknowledging that control over these elements may vary according to the local context.

In the remainder of this review, a brief overview of the pathogen specific epidemiology will be provided, followed by discussion of the cross-cutting five key considerations for implementation.

Pathogen specific overview

The Maternal Neonatal Tetanus Elimination program was the first maternal immunization program to be implemented and is proof of concept for the feasibility and the potential for maternal immunization to reduce neonatal mortality particularly in LMICs. In 1988, the WHO estimated that 787 000 newborns died of neonatal tetanus with an annual global mortality rate of approximately 6.7 deaths per 1000 live births.²¹ In response, the WHO called for elimination of maternal and neonatal tetanus suggesting routine immunization of pregnant women with tetanus toxoid as one of the four components of the strategy.²¹ Between 1999 and 2016, more than 150 million women received at least two doses of tetanus-containing vaccines through this initiative and supplementary vaccination programs.²² As of March 2018, 45 of 59 countries have achieved elimination (less than 1 case per 1000 live births per year), with an estimated 96% reduction in tetanus-related neonatal deaths compared with the late 1980s.^{22,23}

Maternal influenza vaccination has been recommended in the United States (US) since the 1960s.²⁴ Reports from the pandemic influenza in 2009 suggested that pregnant women were at higher risk of complications and adverse neonatal outcomes.^{25–28} However, less is known about the morbidity and mortality associated with seasonal influenza. To try to address this knowledge gap, two systematic reviews were published in 2017.^{29,30} The first suggested that pregnant women are at increased risk of hospitalisation but not of mortality or other adverse outcomes, but 96% of the included studies related to 2009 pandemic influenza.²⁹ The second review found an increased risk of preterm birth with severe pandemic influenza but not with milder illness or with seasonal influenza.³⁰

Following large pertussis epidemics and infant deaths, the US were the first to recommend maternal pertussis vaccination in 2011,³¹ followed by several others.^{32–40} In the United Kingdom (UK), US and Spain impact evaluations have shown an efficacy

of 90% in reducing laboratory-confirmed pertussis, hospitalisations, and deaths in infants.^{41–47}

RSV is the most common cause of acute lower respiratory tract infection in children under five years of age globally, and is estimated to cause more than 30 million infections and nearly 60 000 in-hospital deaths in this age group annually.⁴⁸ Twenty percent of infections and 46% of in-hospital mortality occurs in infants less than six months of age.⁴⁸ However, data is still lacking on the burden of milder disease within the community and out of hospital deaths.⁴⁹

GBS is one of the leading causes of neonatal sepsis and meningitis, with the highest incidence of disease in infants less than three months of age.⁴ An eleven-article supplement was recently published by the GBS Study Team and Expert Advisory Group.⁵⁰ These included the first systematic global estimates of the burden of GBS disease. In this report the prevalence of early-onset infection in infants less than three months of age was estimated to be 205 000 (uncertainty range [UR] 101 000–327 000), and late-onset infection to be 114 000 (UR 44 000–326 000).⁵¹ By their estimates, GBS accounted for more young infant deaths than from mother-to-child transmission of HIV, or of young infant deaths due to RSV, pertussis, and tetanus combined.⁵⁰ The burden of maternal GBS disease has also recently been quantified and presented in the same series by the GBS Expert Advisory Group.⁵⁰ Globally one in five pregnant women are colonised with GBS in either their gastrointestinal or genital tract,⁴ and in 2015 it was estimated that at least 33 000 (UR 13 000–52 000) pregnant or post-partum women experienced GBS sepsis,⁵¹ with an incidence of invasive GBS of 0.38 (95% CI 0.28–0.48) per 1000 pregnancies.⁵² GBS has also been implicated in approximately 15% of cases of chorioamnionitis and 10% of post-partum endometritis in high income settings, but the burden in LMICs is unknown.⁵³ GBS may also contribute to preterm births and possibly up to 10% of stillbirths.⁴

Key considerations for implementation

Information required to decide on the introduction of a new vaccine

When deciding on the priority of introducing a new vaccine, policy makers have to balance this with many other competing health priorities. Information to help inform this decision-making process includes data on disease burden, the efficacy, quality and safety of the vaccine, alternative interventions to prevent disease, and economic and financial implications including cost effectiveness, financial sustainability and programmatic issues.⁵

Data on disease burden

Irrespective of the pathogen, countries' decisions about implementation of a maternal immunization program need to start with an understanding of the local epidemiology and burden of disease, including morbidity and mortality data for the target groups (pregnant women and neonates). This baseline information is critical in evaluating disease prevention priorities, cost-effectiveness analyses and evaluation of the impact should the program be introduced. However, this data is often not available

in resource-constrained settings, and these countries often have to revert to other information sources, for example, from countries with a similar epidemiology.⁵⁴

When all the evidence required to explore the impact of interventions under different scenarios is not available, cost-effectiveness analyses of vaccination programs tend to be based on mathematical modeling. Recognizing the increasing importance of this methodology for informing decision makers, the complexity involved, and the relative lack of studies in this area undertaken in LMICs, the WHO have embarked on a series of consultations to assess the robustness and limitations as well as the generalizability of model estimates to local contexts.⁵⁵ Mathematical models provide a formal framework to examine the effectiveness and cost-effectiveness of different interventions and often translate data from trials into long-term predictions. However, they are based on assumptions in model design that may lead to uncertainty.⁵⁶ In a recently published systematic review of model comparisons in vaccination studies, of 115 eligible studies only 33% followed a systematic approach to identify eligible studies, 25% assessed for quality of study and 3% performed a quantitative synthesis of results.⁵⁷ This highlights the need to standardize mathematical modeling studies.

Data on burden of disease in LMICs is often limited by the lack of specificity of clinical diagnosis, availability of diagnostic testing, access to healthcare, and robust surveillance systems.⁶ One of the advantages of tetanus compared to pertussis, influenza, RSV and GBS is that given the specificity of the clinical syndrome, case definitions rely solely on clinical diagnosis and do not require laboratory confirmation, making reporting of disease burden more available to LMICs.²³ In contrast, accurate diagnosis of RSV or influenza infection usually relies on molecular diagnostic testing.⁵⁸ Many countries, particularly low income countries need improved diagnostic capabilities to be able to gather age-stratified disease data and better characterise burden of influenza disease among pregnant women and infants, and RSV disease among infants. Recognising the importance of this data in a country's decision making process, the WHO published "A Manual for Estimating Disease Burden Associated with Seasonal Influenza" to assist countries to undertake influenza burden of disease research.⁵⁹ With this contribution as well as that of public health agencies (such as the US and European CDC) forming collaborations with LMICs to strengthen influenza surveillance, laboratory-testing, and capacity for disease burden estimation, more robust data from LMICs is emerging.⁶⁰ Similarly, with RSV vaccines on the horizon and to improve the quality of epidemiological data, the RSV Global Epidemiology Network was established with 70 investigators from many LMICs.⁴⁸

Alternative strategies to reduce disease

Given resource limitations, the availability, effectiveness, cost and feasibility of alternative strategies for disease prevention should be considered to determine if maternal immunization is in fact the most cost-effective approach. GBS provides the clearest example of this. The majority of early-onset GBS infections can be prevented with the use of intrapartum antibiotics administered to colonised women,⁴ and the incidence of early-onset

GBS is decreasing in high income countries (HICs) with use of intrapartum antibiotics. However, screening of pregnant women and use of intrapartum antibiotics is a challenging strategy in many LMICs.^{4,53} This strategy requires access to antenatal care, availability of diagnostics, and availability of antibiotics. In addition, given that only 0.5–1% of colonized women give birth to infants who develop early-onset GBS,⁴ many women are exposed to unnecessary antibiotic use and its attendant problems, particularly in relation to antimicrobial resistance. Furthermore, prophylaxis does not reduce the incidence of late-onset GBS disease in infants, and does not prevent maternal infection. These challenges make maternal vaccination an attractive alternative particularly in LMICs. Mathematical modeling has estimated that maternal immunization could prevent up to 57% of GBS disease in various regions of Africa.⁶¹ However prior to introduction of a GBS vaccine, more data on the clinical efficacy, safety, optimal timing of administration, number of doses and co-administration with other vaccines is required.

Recommendations and challenges

The challenges in collecting accurate local epidemiology on burden of disease, particularly in LMICs, limit the capacity of policy-makers in determining the priority of maternal immunization programs, comparing maternal immunization strategies to other existing interventions, and conducting effectiveness and cost-effectiveness analyses. However, much work is being done to strengthen disease surveillance in LMICs and should provide more robust data for future programmatic decisions.

Involvement of pregnant women

Lessons from implementation of maternal influenza and pertussis vaccination in HICs, demonstrate that efforts beyond having national recommendations and evidence of vaccine efficacy and safety are needed to convince pregnant women of the benefit and safety of maternal vaccination to ensure uptake.⁶²⁻⁷¹

While women's vaccine decision-making is frequently motivated more by a desire to protect their baby than for their own benefit,^{72,73} they need to be aware of potential benefits for the mother and the child, as women who do not believe themselves or their infants to be at risk of disease, are less likely to accept vaccination.^{63,64,66,69,70,74} Likewise women who have concerns about the safety of the vaccine, are less likely to accept vaccination.⁷⁵⁻⁷⁷ Since the publication of the WHO Global Advisory Committee on Vaccine Safety in 2014, there have been five published systematic reviews on the safety of influenza vaccination during pregnancy.⁷⁸⁻⁸² All concluded that there were no safety concerns for the mother or the fetus associated with the use of influenza vaccines. There has also been a single published systematic review of the safety of pertussis vaccination during pregnancy which also reported no increase in adverse fetal or neonatal outcomes nor any increase in adverse events following immunization.⁸³ Yet, despite this evidence for vaccine safety, consumers continue to have concerns that limit vaccine uptake.

Furthermore, for successful implementation of new vaccine candidates, such as RSV and GBS, work is required to increase

pregnant women's knowledge of these diseases in addition to reassuring them about the safety and efficacy of the vaccines. Limited awareness of these diseases has been highlighted in two studies from the UK and Canada.^{84,85} The role of healthcare providers in countering pregnant women's concerns by providing information and recommending vaccination, cannot be overstated. Studies have demonstrated that women place most trust in their maternity care providers and so receiving education directly from their providers is likely to be the most effective strategy.^{76,77,86}

Recommendation and challenges

As with any intervention during pregnancy, engagement and education of pregnant women is key to the successful implementation of the intervention. Understanding the multifactorial and complex causes of vaccine hesitancy in different contexts is important to be able to consider approaches at individual, provider, health system and national levels.⁸⁷ Remaining challenges include how to address women from minority groups and those with poor access to healthcare.

Recommendation by healthcare providers

Women may consult obstetricians, midwives, general practitioners, pharmacists, and community health workers during the course of their pregnancy, which provides many opportunities for healthcare providers to discuss vaccination. In 2016 the WHO recommendation for optimal antenatal care was expanded to a minimum of eight antenatal care visits.⁸⁸ While achieving this poses challenges to systems with limited resources and personnel, it provides increased opportunity for discussion and administration of vaccines.

Healthcare providers play three important roles in terms of maternal vaccination (i) providing information and answering women's questions (ii) recommending vaccines, and (iii) where possible providing vaccinations to women within routine maternity care. Healthcare provider recommendation has consistently been demonstrated to be a significant driver of uptake of maternal vaccines.^{64,87,89-93} Therefore understanding the awareness, attitudes and perceptions of healthcare providers and the barriers to healthcare provider recommendation in the local context is vital.

One of the barriers to healthcare provider recommendation to pregnant women is concern about vaccine safety. An example of this is in relation to influenza vaccine. The WHO manual on implementing maternal influenza vaccination, advises that "health worker training and overall communications on maternal influenza vaccination must carefully address safety issues and efficacy information."⁶ Healthcare providers need to be adequately trained about the diseases, the vaccines, vaccination procedure, recognising and reporting of adverse events following immunization (AEFI), and the requirements for uptake and programmatic evaluation.⁶ Educational material needs to be incorporated within resources that are accessible to maternity care providers and within existing training infrastructure wherever practicable.

Where trust in health systems is strong, endorsement of maternal immunization by the relevant health authorities is important in giving healthcare providers confidence to

recommend vaccines.^{6,75,94,95} In addition, having institutional support with policies embedded into guidelines, reminders incorporated into antenatal records, and a clearly outlined procedure for how women should receive vaccination all help to embed vaccination within workplace culture, will assist providers in viewing maternal vaccination as part of routine pregnancy care and as every provider's responsibility.^{75,95,96}

Recommendations and challenges

Healthcare provider recommendation has been shown to be one of the most important determinants of vaccine uptake by pregnant women. Providing healthcare providers with easily accessible, evidence-based and nationally-endorsed guidelines is important. However, having sufficient human resources and adequate time to facilitate these discussions and provision of information related to vaccines, remains a challenge.

Facilitate access and delivery

Improving access to maternal vaccines encompasses availability at a country and programmatic level, access to antenatal care, and provision of vaccination within maternity care settings. The challenges for delivery also need to be considered—maintenance of supply and cold chain, predicting the demand for vaccination, and how future vaccines may be incorporated into the existing model of care.

Vaccine supply

An important component of ensuring access, is maintaining consistent vaccine supply for the predicted demand. This is particularly challenging for influenza vaccine. Currently vaccine composition and expiry date is determined to coincide with the Northern and Southern hemisphere influenza seasons. Tropical and subtropical countries on the other hand often have year round disease. It is therefore foreseeable that these countries will either be pushed to use near-expiring stock expeditiously, use already expired stock, or not vaccinate some eligible women while waiting for new formulations to be available.⁹⁷

One of the goals of the Advancing Maternal Immunization Project of the WHO/PATH is to gain a better understanding of vaccine supply needs and potential demand.⁹⁸ One recently published demand forecasting model used projected data from 2020 to 2029 to simulate demand for seasonal influenza vaccination in 80 LMICs should maternal immunization programs be introduced.⁹⁷ The model is limited by poor quality data on the seasonality of influenza in many LMIC, knowledge of vaccine acceptance amongst pregnant women in these communities, and capacity to predict organizational capacity to implement such programs. However, with these limitations in mind they estimated that supply should meet demand based on 2015 production rates although several countries could face challenges related to production processes and shelf-life. The authors of this study suggest that these could be overcome by extending the expiry date by three months and alternating Northern and Southern hemisphere vaccines to ensure consistent supply.⁹⁷

Strengthening antenatal care

Critical to the successful implementation of a maternal immunization program is a robust antenatal care system. Women who present late in pregnancy may miss the opportunity for timely vaccination and thereby for optimal protection for themselves and their infant. Furthermore while globally 86% of pregnant women access antenatal care with skilled health personnel at least once during their pregnancy,⁹⁹ only 64% of women receive the previously recommended minimum of four antenatal visits during their pregnancy and therefore for many women there are more limited opportunities to discuss maternal vaccinations.⁸⁸ While the reasons for this are complex, financial incentives such as cash transfers or redeemable vouchers have been demonstrated to successfully incentivise antenatal care attendance in various contexts, and could potentially be utilised for the same purpose or also to incentivise vaccination directly.¹⁰⁰

Incorporating vaccination into maternity care

There have been many strategies employed to facilitate vaccination within antenatal care settings. Where a doctor's order has been required for vaccination, removing this requirement with a standing order for midwife or nurse-administered vaccination has been successful in increasing uptake.^{101,102}

Other innovative strategies include use of a dedicated onsite immunization service, deployment of an immunization nurse within antenatal clinics, use of community outreach or immunization services, and pharmacist-delivered vaccination.¹⁰²⁻¹⁰⁴

Whether vaccines are provided within antenatal clinics, through the Expanded Program on Immunization, by primary care, by ancillary services such as HIV care or child health visits or through dedicated outreach services will depend on the capacity of existing services, the optimal strategy for reaching pregnant women, the likely demand for vaccination and ability to incorporate future vaccines into the delivery platform.⁶

Recommendations and challenges

Vaccine supply and integration of immunization into antenatal care services are both important considerations for the success of maternal immunization programs. The structures that have ensured the success of maternal tetanus elimination programs may provide a platform on which to build future maternal vaccination programs. However challenges remain in strengthening antenatal care services, including the linkage between immunization and antenatal care systems.

Surveillance, program evaluation and safety monitoring

Another key factor for successful implementation of maternal immunization programs is a robust system for monitoring vaccine coverage, as well as adverse events following immunization and disease surveillance. These elements can provide both consumers and healthcare workers with reassurance about the safety of a program, monitor for any unexpected safety signals, identify areas of suboptimal coverage for targeted interventions and importantly, measure the impact of the vaccination program on disease burden.⁶

Safety surveillance

As outlined, safety concerns are a significant barrier to health-care provider recommendation and uptake by pregnant women. One issue with safety monitoring of maternal vaccination is the lack of standardised definitions for many obstetric and neonatal outcomes which limits collection and comparison of safety data.^{105,106} In an effort to overcome this barrier, the Global Alliance on Immunization Safety Assessment in Pregnancy (GAIA), as part of the Brighton Collaboration have published 21 case definitions for obstetric and neonatal outcomes.^{107,108} These have been endorsed by the WHO and other regulatory and public health authorities for use in future vaccine trials and post-licensure surveillance in an attempt to harmonise safety reporting.

Surveillance systems already exist to varying degrees within maternal and child health programs in LMICs.^{109,110} However currently they often do not capture serious adverse pregnancy outcomes such as fetal loss, stillbirth, neonatal death, and congenital malformations.¹¹⁰ Data from global passive surveillance systems indicate very limited reporting of AEFIs following maternal immunization from LMICs.¹¹⁰ This has led the WHO to recommend against reliance on passive surveillance systems alone for post-marketing surveillance of any introduced vaccines in LMICs and there is growing interest from international, regional and national authorities, in building capacity for active surveillance systems.¹¹⁰ To increase reporting and raise awareness of the importance of safety monitoring, training and education of healthcare workers and the community in detection and reporting of AEFIs, and strengthening of and linkage of health information systems and pregnancy registries are needed.

Programmatic evaluation

There are three important elements of programmatic evaluation that may also require strengthening prior to, or at the time of, introduction of new maternal vaccines. These are; (1) monitoring of vaccine coverage; (2) measuring impact on maternal and neonatal disease, and (3) evaluation of service delivery.

Ideally, recording of vaccination needs to be integrated into existing antenatal records and pregnancy registries where they exist. Other strategies include recording maternal vaccination on the infant's vaccination card, or periodic immunization coverage surveys, although both of these are prone to recall bias with retrospectively collected data.⁶ In terms of measuring the impact of a maternal vaccination program on disease, it is first necessary to have robust epidemiological data at baseline. The challenges of collecting this data in LMICs has been discussed previously. Finally, the WHO recommends post-introduction evaluation 6–12 months following introduction of any new program along with existing National Immunization Program reviews.⁶ Building capacity for programmatic evaluation is challenging but an essential component of implementation strategy.

Recommendations and challenges

Systems for safety monitoring, disease surveillance and program evaluation are all post-implementation activities but need to be considered in the implementation phase. Many of the challenges

are similar to those of measuring disease burden, including lack of standardised case definitions and quality of data. However with moves by the Brighton collaboration and the WHO to overcome these challenges, there is room for optimism about the increased capacity of LMICs to contribute to our understanding of the impact of maternal immunization programs in reducing neonatal morbidity and mortality.

Conclusion

The Maternal and Neonatal Tetanus Elimination Program serves as proof of concept that with adequate political will and resources, significant reduction in maternal and neonatal mortality can be achieved globally. Both Tetanus and Influenza vaccination programs have helped to identify bottlenecks to vaccine introduction and implementation planning.

To ensure optimal allocation of limited resources, LMICs in particular, will need to prioritize new vaccination programs targeting pregnant women based on the impact they could have on local burden of disease, and implementation-related aspects such as vaccine acceptability, vaccine safety and cost-effectiveness. To inform such a prioritization, additional data on maternal immunization in LMICs is needed. While RSV and GBS vaccines are still either in development or clinical trial stage, accumulating safety and efficacy data will be important as future programs will only achieve high coverage if pregnant women and healthcare providers understand the benefits and can be reassured in relation to the safety of the vaccines. Therefore, careful planning is required along with assessment of the necessary financial and human resource investments.

Global efforts such as the Advancing Maternal Immunization (AMI) project and the WHO's Maternal Immunization and Antenatal Care Situation Analysis (MIACSA) project aim to improve the understanding of current maternal vaccine service delivery in LMICs and to identify optimal pathways and tools for decision-makers and implementers to translate global policies into effective national introduction of new maternal vaccines.^{98,111}

Disclosure of potential conflicts of interest

Philipp Lambach works for the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of the World Health Organization. The authors have no interests to declare.

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