Maternal Immunization: Country Priorities and Market Requirements

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Acronyms

AMRH	African Medicines Regulatory Harmonization
ANC	antenatal care
APEC	Asia-Pacific Economic Cooperation
ASEAN	Association of Southeast Asian Nations
AVAREF	African Vaccine Regulatory Forum
BCG	Bacillus Calmette-Guérin vaccine (tuberculosis vaccine)
BFS	blow-fill-seal
CBER	Center for Biologics Evaluation and Research (United States)
CDRH	Center for Devices and Radiological Health (United States)
CDSCO	Central Drug Standard Control Organization (India)
CE	Conformité Européenne
CFDA	China Food and Drug Administration
cPAD	compact prefilled autodisable device
DSJI	disposable-syringe jet injector
EMA	European Medicines Agency
EPI	Expanded Programme on Immunization
FDA	Food and Drug Administration (United States)
GBD	Global Burden of Disease
GBS	group B streptococcus
Hib	*Haemophilus influenzae* type b
HPV	human papillomavirus
ID	intradermal
IIV	inactivated influenza vaccine
IPV	inactivated poliovirus vaccine
LAIV	live attenuated influenza vaccine
LMIC	low- and middle-income country
MAP	microarray patch
MCC	Medicines Control Council (South Africa)
MMR	measles-mumps-rubella

NRA	National Regulatory Authority
PCV	pneumococcal vaccine
PMOA	primary mode of action
PPB	Pharmacy and Poisons Board (Kenya)
PQ	prequalification
RSV	respiratory syncytial virus
SRA	stringent regulatory authority
TAM	total available market
Tdap	tetanus toxoid, diphtheria, and acellular pertussis
TT	tetanus toxoid
UNICEF	United Nations Children's Fund
USD	US dollar
VPPAG	Vaccine Presentation and Packaging Advisory Group
WHO	World Health Organization

Executive summary

Although there has been a dramatic reduction in under-5 deaths in the past 20 years, today's neonatal mortality accounts for a higher proportion of total deaths in that age group—44 percent. In response, maternal immunization is gaining momentum as a global health priority. New vaccines are under development and available vaccines are under consideration for inclusion in routine antenatal care (ANC). Maternal immunization achieves two objectives: protecting both the pregnant woman and her newborn from vaccine-preventable diseases. Data and information related to the safety, efficacy, and cost-effectiveness of available or pipeline vaccines will be needed to inform decision-making by low- and middle-income countries (LMICs) to invest in and implement maternal immunization strategies. This understanding will also be critical to identifying the potential of vaccine delivery and packaging technologies to improve upon both the current and future state of maternal immunizations with select and high-priority vaccines. Opportunities may exist to integrate such technologies into different presentations and delivery formats of maternal immunization vaccines to help better achieve global public health objectives and goals. To date, a number of different packaging and delivery technologies have been developed to improve safety, efficacy, cost- and program effectiveness, and ease of administration, as well as other potential program benefits. Technology examples include compact prefilled autodisable devices (cPADs), microarray patches (MAPs), and intradermal (ID)-capable technologies such as the ID adapter and disposable-syringe jet injectors (DSJIs).

This report presents the results of primary and secondary research that provides insight into countries' top priorities for maternal immunization and characterizes the market for adult immunizations in select LMICs. It outlines the landscape of vaccines with known and potential value in maternal immunization, summarizes global stakeholder and country-level program priorities for maternal immunization programs, provides demand estimates for high-priority maternal vaccines, and summarizes regulatory requirements. The results are from both desk research and in-country surveys.

Key findings: Maternal immunization—disease burden and status

Estimates of the burden of diseases preventable by maternal vaccination show that the largest of these killers of children between 0 and 27 days old are related to *Haemophilus influenzae* type b (Hib), pneumococcus, and tetanus. Because data on the impact of maternal vaccination on neonatal health outcomes are limited to the few vaccines now in use, countries need to conduct robust surveillance to gather the following data for maternal immunization: (1) safety for mother and fetus, (2) efficacy through placental transfer of antibodies, and (3) effectiveness in averted morbidity.

Global maternal immunization efforts have intensified in recent years, with 84 projects listed under the World Health Organization Maternal Immunization Research and Implementation Portfolio. A recent meeting of experts and key stakeholders highlighted the need for (1) detailed surveillance data on neonatal morbidity outcomes, (2) encouraging integration of maternal immunization into ANC services while exploring other integration options, (3) building maternal immunization target product profiles, and (4) integrating maternal immunization into World Health Organization (WHO) guidance for ANC services.

An in-country survey conducted in LMICs provided information on the priorities that inform maternal vaccine programming at the national level. Eleven of 14 countries reported a dedicated maternal

immunization policy or program, which typically was integrated into existing health programs. Tetanus toxoid (TT) was the most frequently included free-of-charge vaccine, with coverage rates ranging between 41 percent and 60 percent.

Key barriers identified by participants were lack of access to services, low awareness of the value of vaccination during pregnancy, concerns about fetal safety, and low participation in ANC. Integration of maternal immunization services into standard ANC services may help alleviate some of these barriers, while developing vaccine presentations suitable for community-based and home-based care may improve reach into populations with limited access to ANC services.

Key findings: Maternal immunization vaccines—status and challenges

The top five high-priority vaccines for addressing maternal and neonatal burden of disease identified by global-level stakeholders are tetanus toxoid (TT), inactivated influenza vaccine (IIV), group B streptococcus (GBS), respiratory syncytial virus (RSV), and pertussis vaccines. However, among stakeholders at the country level, these priorities shift to include hepatitis B vaccine rather than RSV as a high-priority vaccine among those that are already prequalified and to exclude GBS vaccine among those that are still in development. Country-level stakeholders also identify malaria, hepatitis C, and dengue as high-priority diseases without currently prequalified vaccines.

The global market for these high-priority vaccines is large. Calculations using data from the World Bank show that the total available market (TAM) for maternal vaccines from 2016 to 2025 is 1.37 billion women. Using the coverage rate for TT vaccine, the likely demand for maternal vaccines for the time period will be at least 1.16 billion doses of each vaccine included in global maternal immunization strategies. However, this projection will vary depending on the speed with which new vaccines are introduced into maternal immunization strategies globally.

Regulatory requirements can pose barriers to implementation of maternal vaccinations. The capacity of national regulatory authorities (NRAs) in LMICs is generally limited, and guidance on labeling vaccines for use in special high-risk populations such as pregnant women can be vague or nonexistent. This impedes product development, approval, and launch. Maternal vaccines present unique regulatory challenges because safety and efficacy must be considered for the mother, fetus, and newborn.

With maternal immunization gaining momentum as a global health priority, a robust evidence base will be needed to encourage LMICs to invest in strengthening their maternal immunization strategies. When other vaccines become available, such as those for RSV, malaria, or GBS, these countries will need help in navigating regulatory approval and in launching vaccines for use.

Introduction

According to the World Health Organization (WHO), the neonatal period—the first 28 days of life—is the most vulnerable time for a child's survival. Several factors are cited for the large number of neonatal deaths in the poorest countries of the world, including a lack of health services that are available to pregnant women and newborns.[1] Maternal immunization is one such service, and it has been demonstrated that maternal vaccination against tetanus and influenza improves the health of newborns and protects neonates from infection-related causes of death.[2,3,4,5,6] Maternal vaccination has the potential to protect the baby not only indirectly by protecting the mother but also directly through transplacental transfer of maternal immunoglobulin G.[7] The two most widely used vaccines for pregnant mothers are the inactivated influenza and TT vaccines. Both have been shown to protect newborn children and are recommended by the United States Centers for Disease Control and Prevention and WHO. Despite this evidence, the implementation of maternal immunization programs and uptake of vaccines have seen limited success in low- and middle-income countries (LMICs).[2,3,4,5]

Successful childhood immunization programs in LMICs provide insights into the factors that have improved vaccine coverage.[8] Since the inception of the Expanded Programme on Immunization (EPI) 40 years ago, childhood vaccination has grown from less than 5 percent coverage to approximately 83 percent coverage.[9] This increase reflects improvements to systems for managing the procurement, storage, transport, and delivery of childhood vaccines. New vaccine presentations have also improved uptake: combining vaccines into multivalent formats has reduced the work burden for health care providers, the number of times a patient must visit the clinic, and the number of injections at each visit. Single-dose packaging, compact prefilled autodisable devices (cPADs), and auto-disable syringes have reduced training requirements and risks to health care workers and the surrounding communities, enabling minimally trained providers to deliver certain vaccines. Microarray patches (MAPs), intradermal (ID) syringe adapters, and disposable-syringe jet injectors (DSJIs) can address barriers to delivering childhood immunizations in a variety of resource-poor settings where conventional delivery is not reaching all children. These innovative technologies and approaches were developed in part to address constraints unique to delivering vaccines to children in LMICs.

PATH project: Novel packaging and delivery technologies for maternal vaccines

As maternal immunization programs expand and gain more attention globally, the development of new vaccines specifically for use in pregnancy, such as respiratory syncytial virus (RSV), is becoming an innovation arena with potentially high public health impact. It will be important to have a detailed understanding of the relationship between the market requirements for new vaccines, programmatic priorities of countries introducing them, and possible barriers—personal, programmatic, and regulatory—in new scenarios of use that may constrain successful uptake. Assessments of these factors will allow stakeholders to use the most appropriate strategies to ensure high coverage. To address some aspects of this need for evidence, PATH is working to identify possible opportunities to optimize vaccine presentation and packaging for maternal immunization scenarios through funding from the Pfizer Independent Grants for Learning & Change. This work is undertaken through primary and secondary research under Objective 1 of the Novel Packaging and Delivery Technologies for Maternal Vaccines Project, followed by field research in two countries under Objective 2, and a technology mapping exercise under Objective 3. The project work focuses on six countries—China, India, Kenya, Senegal,

South Africa, and Vietnam—selected to represent a spectrum of LMICs with varying approaches to maternal immunization across three WHO regions.

This report presents the results of Objective 1: Determine the current state of the market for maternal immunizations and assess stakeholder requirements. The data presented here were collected through primary and secondary research conducted to provide insight into countries' top priorities for maternal immunization and to characterize the market for adult immunizations in select LMICs. The report outlines the landscape of vaccines with known and potential value in maternal immunization, summarizes global stakeholder and country-level program priorities for maternal immunization programs, provides demand estimates for priority maternal vaccines, and summarizes regulatory requirements for maternal vaccination. The results are from both desk research and in-country surveys. The outcomes of this work will inform the design of activities for Objective 2: Characterize maternal immunization delivery scenarios and identify constraints to increased coverage, and Objective 3: Map packaging and delivery technologies to address requirements and constraints identified under Objectives 1 and 2.

Background: The case for maternal immunization

In 2013, the last year for which there are complete data, 2.8 million infants died in their first month of life.[10] Even with the dramatic reduction in under-5 deaths in the past 20 years, today's neonatal mortality accounts for a higher proportion of total under-5 deaths, rising from 37 percent in 1990 to 44 percent in 2013(Figure 1). [10]

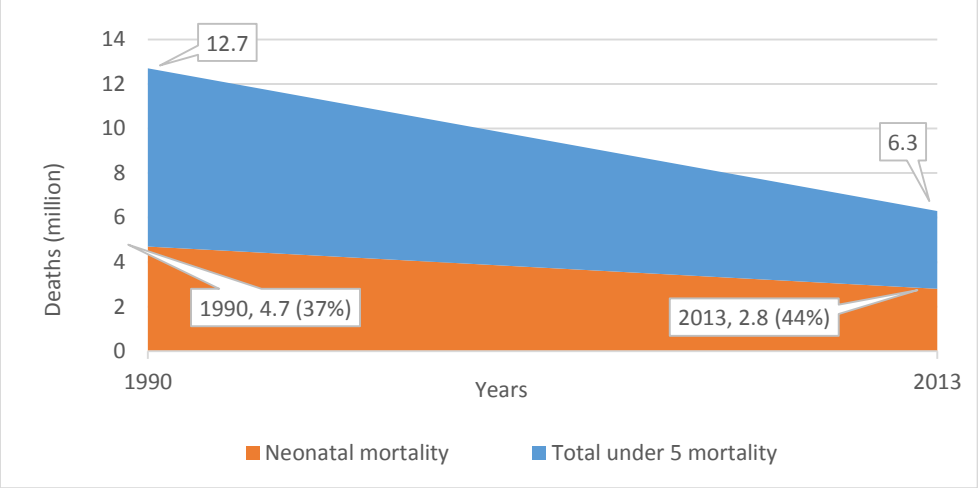


Figure 1. Neonatal mortality as a proportion of total under-5 mortality, 1990 and 2013.

Of the 2.8 million neonatal deaths in 2013, cumulatively, 23 percent were due to the follow causes: sepsis (15 percent), pneumonia (5 percent), tetanus (2 percent), and diarrhea (1 percent) (Figure 1).[a11] However, data on the root causes of neonatal mortality and morbidity hidden within these broader categories are less readily available. Sepsis, for example, has a complex etiology, with several factors that can be prevented by vaccines such as *Haemophilus influenzae* type b (Hib) vaccine, pneumococcal

[a] Due to limitations in how morbidity and mortality data are aggregated across age ranges, mortality is used here as a more robust measure of overall disease burden.

vaccine (PCV), and meningococcal vaccine. Other conditions that may result in or be diagnosed as sepsis, such as group B streptococcus (GBS) and malaria, have vaccines in development.[12,13] These too, when available for use in pregnancy, may reduce the disease burden attributed to sepsis.

To estimate the burden of disease preventable by maternal vaccination, data from WHO, United Nations Children's Fund (UNICEF), and the Global Burden of Disease (GBD) data compiled by the Institute for Health Metrics and Evaluation were reviewed.[14] Although maternal antibodies have been shown to protect children to approximately 6 months of age for some antigens, due to the age breakdown of the key data sets available for this analysis, the age group used here is infants between 0 and 27 days old. We selected available indicators from the GBD data for the disease indications of the vaccines listed in Table 1. Diseases that can be prevented by vaccines listed as under investigation, under development, or contraindicated were excluded from the analysis using GBD data.

Based on the GBD data from 2010, the largest killers of children between 0 and 27 days old globally that are preventable through maternal vaccination are related to Hib (54,140), pneumococcus (41,401), and tetanus (40,467). In the six focus countries, it is estimated that 22,005 neonates died from vaccine-preventable causes in 2010. For infants between 0 and 27 days old, the main vaccine-preventable causes of death in these countries were tetanus (11,558), encephalitis (5,178), and Hib (2,918).[15]

Similarly, because many preterm births are the outcome of infections such as influenza or malaria during pregnancy, cause-specific prevention through maternal immunization could address part of the 965,000 deaths associated with complications resulting from prematurity. For example, influenza has known health risks to women during pregnancy.[16,17] Mothers who have had flu (or respiratory infection during flu season) are significantly more likely to lose the pregnancy or have low-birthweight babies, stillbirths, and preterm deliveries.[16]

Currently, data on the impact of maternal vaccination on neonatal health outcomes are limited to a few vaccines, as noted in the vaccine landscape section below. Quantifying the need for maternal vaccines through robust surveillance of neonatal health outcomes will help drive demand for specific vaccines to be used during pregnancy. With maternal immunization gaining momentum as a global health priority, new research into the potential safety, efficacy, and cost-effectiveness of available vaccines will be needed to encourage LMICs to invest in strengthening their maternal immunization strategies.

Landscape of vaccines with potential applications to maternal immunization

Currently, WHO recommends immunization during pregnancy with tetanus toxoid (TT) vaccine and inactivated influenza vaccine (IIV). In LMICs, TT is currently the only vaccine that is used extensively during antenatal care (ANC).[18] In the United States and the United Kingdom, TT is delivered in combination with diphtheria and acellular pertussis in the form of a combined vaccine (tetanus toxoid, diphtheria, and acellular pertussis or Tdap), but this combination vaccine is not used extensively in LMICs.[19] Beyond these vaccines, recommendations for existing vaccines for use in pregnancy are sparse and inconsistent, due primarily to lack of high-quality evidence supporting (1) safety for mother and fetus, (2) efficacy through placental transfer of antibodies, or (3) effectiveness in averted morbidity.[19] In addition, some vaccines are contraindicated during pregnancy due to the inclusion of live virus, such as live attenuated influenza vaccine (LAIV) and Bacillus Calmette-Guérin.[20] However, no data have

demonstrated a threat to maternal or fetal safety for these vaccines, and surveillance data on inadvertent vaccination using live-virus vaccines during pregnancy have not reported adverse pregnancy outcomes in these events.[19]

In fact, there are vaccines such as measles-mumps-rubella (MMR) that can confer protection through maternal antibodies when the mother is vaccinated before pregnancy. There also are other vaccines that protect an infant from exposure by protecting the mother from contracting a disease; this is known as the cocooning effect. For example, measles and rubella vaccines should be given prior to pregnancy and are well known to provide protection to newborns through maternal antibodies. Rubella vaccination, in particular, is primarily given to prevent birth defects that occur due to infection during pregnancy. Likewise, the value of maternal pertussis vaccination is from not only maternal antibodies but also the cocooning effect, which would help to prevent the 66 percent of infant pertussis cases that are caused by family members.[21]

A summary of vaccines and their status related to maternal immunization recommendations is presented in Table 1.

Table 1. Vaccines and indications during pregnancy.[α]

Vaccine	Formulation/ delivery route	Available packaging options	Recommended during pregnancy	Safety in pregnancy documented	Antibody duration in infant
WHO prequalified					
Cholera	Liquid/oral	Vial, vial + buffer sachet	If indicated	ND	ND
Haemophilus influenzae type b: conjugate/ polysaccharide	Liquid, lyophilized/ IM, SC	Vial, vial + ampoule (diluent), vial + vial	If indicated	Yes	2 months
Hepatitis A	Liquid/IM	Vial, prefilled syringe	If indicated	Yes	ND
Hepatitis B	Liquid/IM	Vial, Uniject™, ampoule, prefilled syringe	If indicated	Yes	ND
Inactivated poliovirus	Liquid/IM, SC	Vial, prefilled syringe	If indicated	Yes	ND
Influenza (IIV)[b]	Liquid/IM, SC, ID	Vial, vial + vial (adjuvant), prefilled syringe	Routinely recommended	Yes	2–3 months
Japanese encephalitis	Liquid, lyophilized/ IM, SC	Vial, prefilled syringe	If indicated	ND	ND
Meningococcal: conjugate/ polysaccharide	Lyophilized + diluent/SC	Vial + vial (diluent)	If indicated	Yes	2–4 months

[b] Inactivated influenza vaccine.

Oral poliovirus	Liquid/oral	Vial, dropper tube	If indicated	Yes	ND
Pneumococcal vaccines (PCV13 and PPSV23)	Liquid/IM	Vial, prefilled syringe	If indicated	Yes	5 months
Rabies	Liquid, lyophilized + diluent/IM, ID	Vial, prefilled syringe, vial + ampoule (diluent)	If indicated	Yes	ND
Tdap	Liquid/IM	Vial, prefilled syringe	Routinely recommended	Yes	2 months for pertussis
TT	Liquid/IM	Vial, Uniject™, ampoule	Routinely recommended	Yes	2 months
Typhoid	Liquid/IM	Vial, prefilled syringe	If indicated	ND	ND
Yellow fever	Lyophilized + diluent/IM, SC	Vial, ampoule + ampoule (diluent), vial + vial (diluent)	If indicated	Unclear	ND
Under investigation (Phase III clinical trial or postmarket surveillance, not prequalified)					
Cytomegalovirus	ND	ND	ND	ND	ND
Dengue	ND	ND	ND	ND	ND
Group B streptococcus	ND	ND	ND	ND	ND
Hepatitis E	ND	ND	ND	ND	ND
Malaria	ND	ND	ND	ND	ND
Respiratory syncytial virus	ND	ND	ND	ND	ND
Under development (pre-Phase III clinical trial)					
Cytomegalovirus	ND	ND	ND	ND	ND
Group A strep	ND	ND	ND	ND	ND
Helminth	ND	ND	ND	ND	ND
Hepatitis C	ND	ND	ND	ND	ND
Herpes simplex virus	ND	ND	ND	ND	ND
Leishmaniasis	ND	ND	ND	ND	ND
Contraindicated					
BCG	Lyophilized/ ID	Vial + ampoule (diluent), ampoule + ampoule (diluent), vial + vial (diluent)	No	ND	ND
Human papillomavirus	Liquid/IM	Vial	No	ND	ND
Influenza (LAIV)	Liquid/nasal (spray)	Prefilled syringe	No	Yes*	ND

MMR* / Rubella	Lyophilized/ SC	Vial + ampoule (diluent), vial + vial (diluent)	No	Yes*	ND
Varicella	Lyophilized/ SC	Vial + vial (diluent)	No	Yes*	ND
Zoster	Lyophilized/ SC	Vial + vial (diluent)	No	Yes*	ND

[α]*Adapted from Chu & Englund, 2015, supplemented by data from CDC Guidelines for Vaccinating Pregnant Women.*[22]
ND refers to studies of protection conferred by vaccination specifically during pregnancy.
**No adverse events have been recorded in surveillance of women inadvertently vaccinated during pregnancy.*
Note: BCG, Bacillus Calmette-Guérin; IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; MMR, measles-mumps-rubella; ND, no data; Tdap, tetanus toxoid, diphtheria, and acellular pertussis; TT, tetanus toxoid.

Global efforts in maternal immunization

Among global development agencies and guidance bodies, maternal immunization efforts have intensified in recent years. The Initiative for Vaccine Research within WHO recently released the first Maternal Immunization Research and Implementation Portfolio, a survey of global activities related to maternal immunization.[23] The portfolio comprises 84 different activities undertaken by more than 50 institutions. Activities are related to strengthening the body of evidence for maternal immunization, such as vaccine trials, implementation research, program development, evidence generation, and monitoring and evaluation efforts. The majority of entries in the portfolio highlight the focus on evidence generation (57 of 80 separate projects), illustrating the global push across major policy and research institutes to span the gulf between suspected benefits and demonstrated data supporting use of maternal vaccines to address neonatal health outcomes.

A count of projects by vaccine, listed in Table 2, illustrates the breadth of vaccine research, implementation research, and policy development projects ongoing globally. Of the 84 projects listed, 48 have a focus on influenza, indicating it as a strong-priority investment among global stakeholders in the field of maternal immunization. Pertussis (16), RSV (14), and Tdap (13) are also focus areas for global efforts.

Table 2. Frequency of vaccine-specific projects in the WHO Maternal Immunization Research and Implementation Portfolio.

Vaccine	Number of projects
Influenza	48
Pertussis	16
RSV	14
Tdap	13
GBS	6
Malaria	4
HPV	3
PCV	3
TT	2
Rotavirus	2
MMR	1
IPV	1
Rabies	1
Shigella	1

In addition, GBS vaccine is gaining attention in the literature and among key global stakeholders. In January 2015, the Bill & Melinda Gates Foundation convened key experts and stakeholders in maternal immunization for a meeting to discuss challenges, priorities, and strategies. The Foundation listed GBS as one of five of its high-priority vaccines, along with influenza, TT, pertussis, and RSV.[17] With the inclusion of GBS in the global agenda for maternal immunization, an increase in projects targeting GBS can be expected.

Along with outlining high-priority vaccines on the global agenda, the members of the meeting discussed key challenges of achieving robust coverage for maternal immunization. They highlighted the need for detailed surveillance data on neonatal morbidity outcomes, encouraging integration of maternal immunization into antenatal care (ANC) services while exploring other appealing integration options, building maternal immunization target product profiles, and integrating maternal immunization into WHO guidance for ANC services.[17]

Survey of country priorities for maternal immunization

Background

Although global disease burden in the neonatal age group is an important factor in characterizing potential needs for maternal immunization, the maternal and child health priorities of individual countries will ultimately drive their policy, planning, and purchasing decisions. In a recent commentary on the state of maternal immunization, Janet Englund wrote that although there is increasing acceptance and interest in promoting maternal immunization to prevent a wide range of neonatal infections, the additional burden on prenatal care programs and health systems in LMICs must be addressed.[24] This will require an understanding of current practices and future priorities for country-level implementation of maternal immunization plans.

To illuminate the priorities that inform maternal vaccine programming at the national level, PATH developed and conducted a survey aimed at national-level stakeholders and decision-makers in key countries. The survey included themes of national policies and strategies, current and target coverage rates, barriers to the expansion of maternal immunization, priorities for future vaccines, and the integration of maternal immunization into the health system. These themes were identified through a literature review and in consultation with expert advisors at PATH. Questions regarding barriers to the expansion of maternal immunization were based on a framework of factors affecting maternal immunization in developing countries, which were presented in a key paper by Pathirana et al.[18]

Methods

We used a network sampling strategy to identify appropriate survey participants in target countries. Six LMICs were selected initially for their representation of different economic levels, immunization strategies and priorities, and geographic locations within the project scope. These were Kenya, Senegal, South Africa, China, India, and Vietnam. At the recommendation of PATH maternal health and vaccine experts, we supplemented the data collected from these by inviting representatives from the following nine additional countries to participate in the survey: Thailand, Guatemala, Peru, The Gambia, Guinea, Rwanda, Uganda, Somalia, and South Sudan. Countries are listed according to income in Table 3.

Table 3. Surveyed countries by income level.

Lower income	Middle income
The Gambia	China
Guinea	Guatemala
Kenya	India
Rwanda	Peru
Somalia	South Africa
South Sudan	Thailand
Uganda	Vietnam

The survey was designed to collect data on national maternal immunization strategies, rather than on individual stakeholders' opinions; therefore, the sampling strategy did not include a target sample size but rather focused on obtaining representation from a breadth of countries. In most cases, multiple respondents per country were contacted to ensure at least one response from each country.

Following review by the PATH Research Determination Committee, the survey was determined to not be human subjects research, indicating no further ethical review would be required. The survey was then administered by a combination of a web-based format and an emailed document; the emailed document was then transferred to the web-based form for ease of analysis. A copy of the survey is included as Appendix 1.

Results

Of the representatives from 15 countries that were invited to participate in the survey, only Senegal did not return a response; thus, the N for most analyses was 14. Two countries, China and Vietnam, returned multiple responses; so for these, one primary respondent was selected based on the expertise of respondents and completeness and consistency of data, and secondary responses were used to

validate or supplement the primary respondent's data. Country-specific summaries, including programmatic priorities, country-specific disease burden data, and a regulatory synopsis, are included as Appendix 2.

Respondents

Survey responses came from individuals working within ministries of health, national immunization programs, and national and international nongovernmental organizations, including UNICEF and WHO. Most respondents (11/14) identified themselves as technical experts/advisors in immunization or maternal and child health. The remaining three identified as health systems experts (2) and a consultant (1). Participants reported an average of 11.8 years working in the field of maternal immunization.

Snapshot of maternal immunization strategies

Among the respondents, 11 of 14 reported that their countries had a dedicated maternal immunization policy or program. With the exception of The Gambia, all have been in place for more than five years. Participants from Kenya, Somalia, and South Sudan reported that their countries have no formal maternal immunization policy or programs; however, in Kenya the overall national strategic health plan includes the elimination of maternal and neonatal tetanus and provides TT at no cost to pregnant women.[25] For the most part, maternal immunization strategies were integrated into existing health programs. Only The Gambia, Rwanda, and Guatemala indicated that their maternal immunization programs were not integrated with other public health programs (Rwanda has a maternal immunization program integrated into refugee settings). Of the 11 with integrated maternal immunization strategies, 5 were integrated into EPI and 6 were integrated with maternal and child health programs. Elements of the respondent countries' maternal immunization policies are presented in Table 4.

Table 4. Maternal immunization policies in survey respondents' countries.

Country	Maternal immunization policy status	Included vaccines (recommended and free)
Lower income		
The Gambia	Yes; < 5 years.* Standalone policy within national health strategy.	TT, IIV
Guinea	Yes; > 5 years.	IIV
Kenya	No, but elimination of maternal & neonatal tetanus is part of the national health strategy and TT is provided free to all pregnant women.	TT
Rwanda	Yes; > 5 years. Integrated with EPI.	TT
Somalia	None	None
South Sudan	None	None
Uganda	Yes; > 5 years. Integrated with EPI.	TT
Middle income		
China	Yes; > 5 years. Integrated with EPI.	Tdap, meningococcal, hepatitis A, hepatitis B, JE, OPV
Guatemala	Yes; > 5 years. Standalone policy within national health strategy.	TT
India	Yes; > 5 years. Integrated with EPI.	TT

Peru	Yes; > 5 years. Integrated with maternal and child health program.	IIV, TT
South Africa	Yes; > 5 years. Integrated with maternal and child health program.	TT
Thailand	Yes; > 5 years. Integrated with maternal and child health program.	Tdap, TT, hepatitis B, JE, OPV
Vietnam	Yes; > 5 years. Integrated with maternal and child health program.	TT, Hib, Typhoid, Cholera, hepatitis B, JE, OPV
* Respondents were asked if their countries maternal immunization policies have been in place for greater than 5 years or less than 5 years in order to gauge how well established the maternal immunization strategy is within the country.		

The countries with the highest number of free vaccines included as part of maternal immunization strategies were all in the WHO Western Pacific Regional Office/Southeast Asia Regional Office regions: Vietnam (7), China (6), and Thailand (5). India, the only other Asian country included in this survey, only offers TT for free. Among the five WHO Regional Office for African countries with formal maternal immunization strategies, The Gambia is the only one to offer two free vaccines (IIV and TT). TT is the only free maternal vaccine offered in Rwanda, South Africa, and Uganda, and Guinea offers only IIV for free. Within the Pan American Health Organization region, Peru offers TT and IIV for free, and Guatemala offers only TT.

For the 11 countries with maternal immunization policies, TT topped the list as the most frequently included free-of-charge vaccine (7 countries), and all but Guinea offer either TT or Tdap for free as part of their maternal vaccine strategy. Conversely, Guinea provides IIV for free, as do Peru and The Gambia (China recommends flu vaccine but does not offer it for free). Figure 2 illustrates the frequency with which vaccines were included in countries' maternal immunization strategies among the 11 countries reporting a formalized strategy.

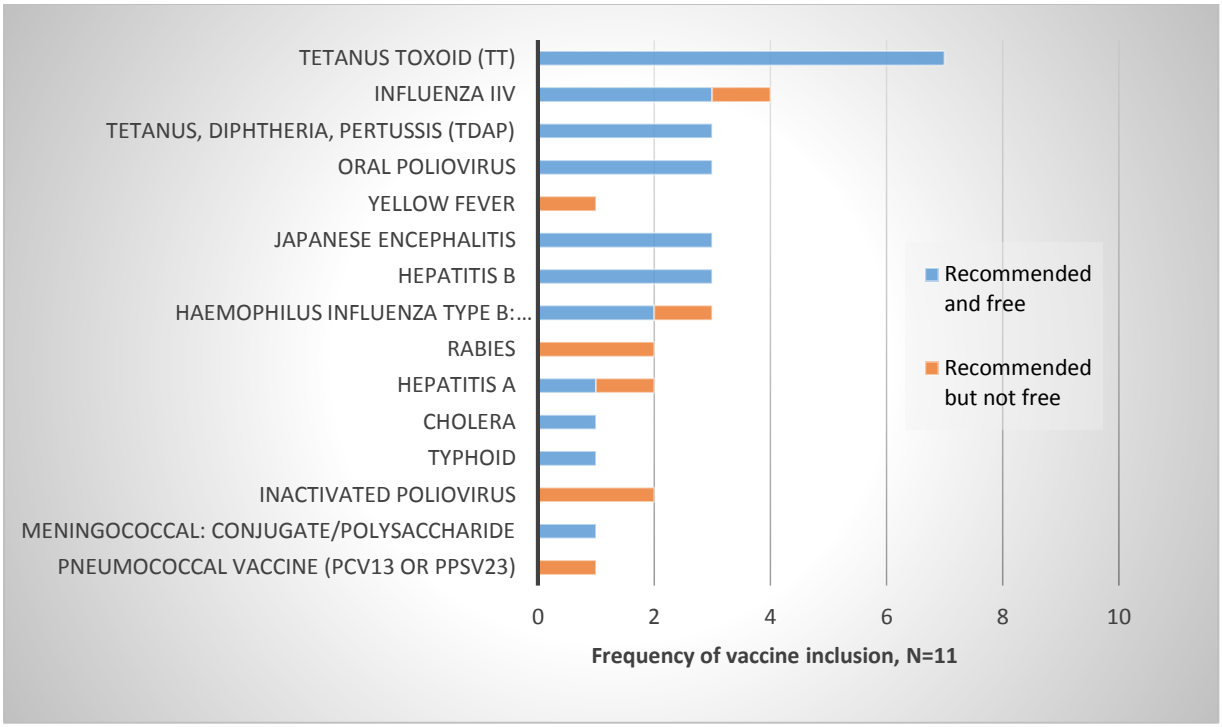


Figure 2. Vaccines included in immunization strategies in countries participating in the survey.
Note: IIV, inactivated influenza vaccine.

Coverage rates varied substantially among countries and among vaccines. For example, among the seven countries including TT as a free vaccine, coverage ranged between 41 percent and 60 percent. Notably, few participants provided estimates of coverage of those vaccines included in their national policies, indicating that coverage rates are not well known even among country experts. Respondents provided some information on how maternal immunizations are monitored within each country, with eight indicating that monitoring occurred through regular reporting mechanisms. Another two respondents described intermittent site visits or periodic surveys as a monitoring mechanism, and three countries reported that maternal immunizations were not monitored through any formal mechanism.

Maternal immunization at public and private facilities

Participants indicated that public facilities are the primary sites for the delivery of maternal immunization services. These include primary health care facilities, specialized ANC facilities, health posts, community health centers, and hospitals. In Kenya, the participants mentioned that maternal immunizations are also available through faith-based organizations and private health facilities. Health care workers in these facilities who are primarily responsible for providing maternal vaccinations include nurses, midwives, and doctors.

When asked about the difference between maternal immunizations in public and private health systems, respondents' answers varied substantially by country. Participants from China, India, Kenya, South Africa, and Uganda suggested that there was little difference between the two systems. Respondents from Guatemala, Rwanda, and South Sudan indicated that at private facilities, immunizations may cost more but are delivered by better-trained staff. In The Gambia, private health care providers are unlikely to administer vaccines to pregnant women. With the exceptions of

Guatemala and South Sudan, all countries reported high rates of women seeking care during pregnancy. Ten respondents suggested that health care providers recommend immunization to pregnant mothers, rather than women seeking out vaccination themselves.

Barriers to achieving optimal maternal vaccine coverage

Participants were asked to describe barriers impeding optimal coverage of maternal vaccination within their countries. Multiple participants highlighted the lack of access to marginal populations as a key barrier, as well as other patient-related barriers such as lack of patient awareness and social mobilization, generally low ANC participation and decision-making skills among patients, and low vaccine acceptance among pregnant women. When specifying issues related to women's access to maternal vaccines, respondents ranked reasons why pregnant women and their families may not seek out or accept vaccination during pregnancy. Concern regarding fetal safety was the most frequently cited (5/10), followed by lack of awareness and inconvenience (3/10 each). Other barriers included cost, religious beliefs, myths about vaccinations, local superstitions and traditions, and lack of knowledge regarding potential risks and benefits.

Country programmatic priorities for maternal immunization

Respondents were asked to rank the programmatic areas listed in Figure 3 by priority for their country's maternal immunization strategy. Each topic was assigned a weight. Responses were then weighted according to the corresponding weight of the ranking to identify priorities common across respondent countries. Increasing demand among pregnant women scored highest across the seven options, with 6 (of 14) countries listing this as the highest priority and an additional 2 countries listing it as a secondary priority. Setting maternal immunization policy was also selected as a high-priority option frequently. On average, the least important activities were expanding coverage of specific vaccines and introducing new vaccines.

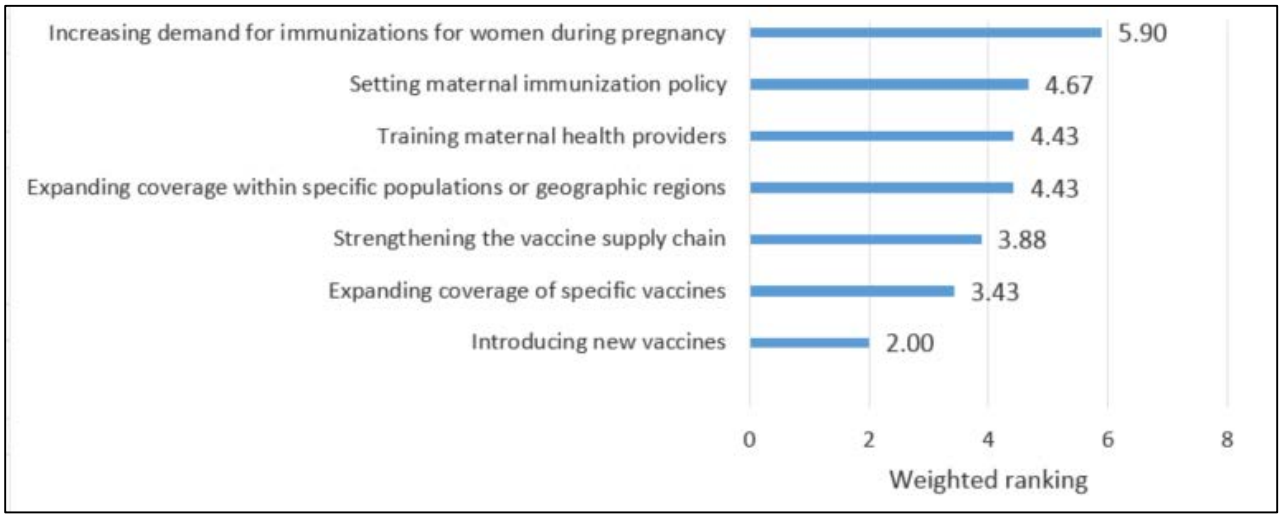


Figure 3. Weighted ranking of high-priority programmatic issues for maternal immunization.

Priorities in addition to those in Figure 3 included better integration with reproductive health programs, a comprehensive care package for pregnant women that includes maternal immunization, inclusion of campaigns for maternal immunizations, and strengthening of the cold chain.

High-priority vaccines for inclusion in maternal immunization programs

Among the country respondents, for diseases with vaccines that have WHO prequalification (PQ) and are commercially available as of the date of this report, hepatitis B was selected most frequently as a high-priority vaccine for their maternal immunization program. Aligning with WHO and other global institutions' high-priority areas of focus, respondents indicated that TT and IIV are also high-priority currently available vaccines, while malaria, hepatitis C, and dengue topped the list of diseases with no current prequalified vaccine. A complete list of commercially available vaccines, ranked by priority across all country responses, is included in Figures 4 and 5.

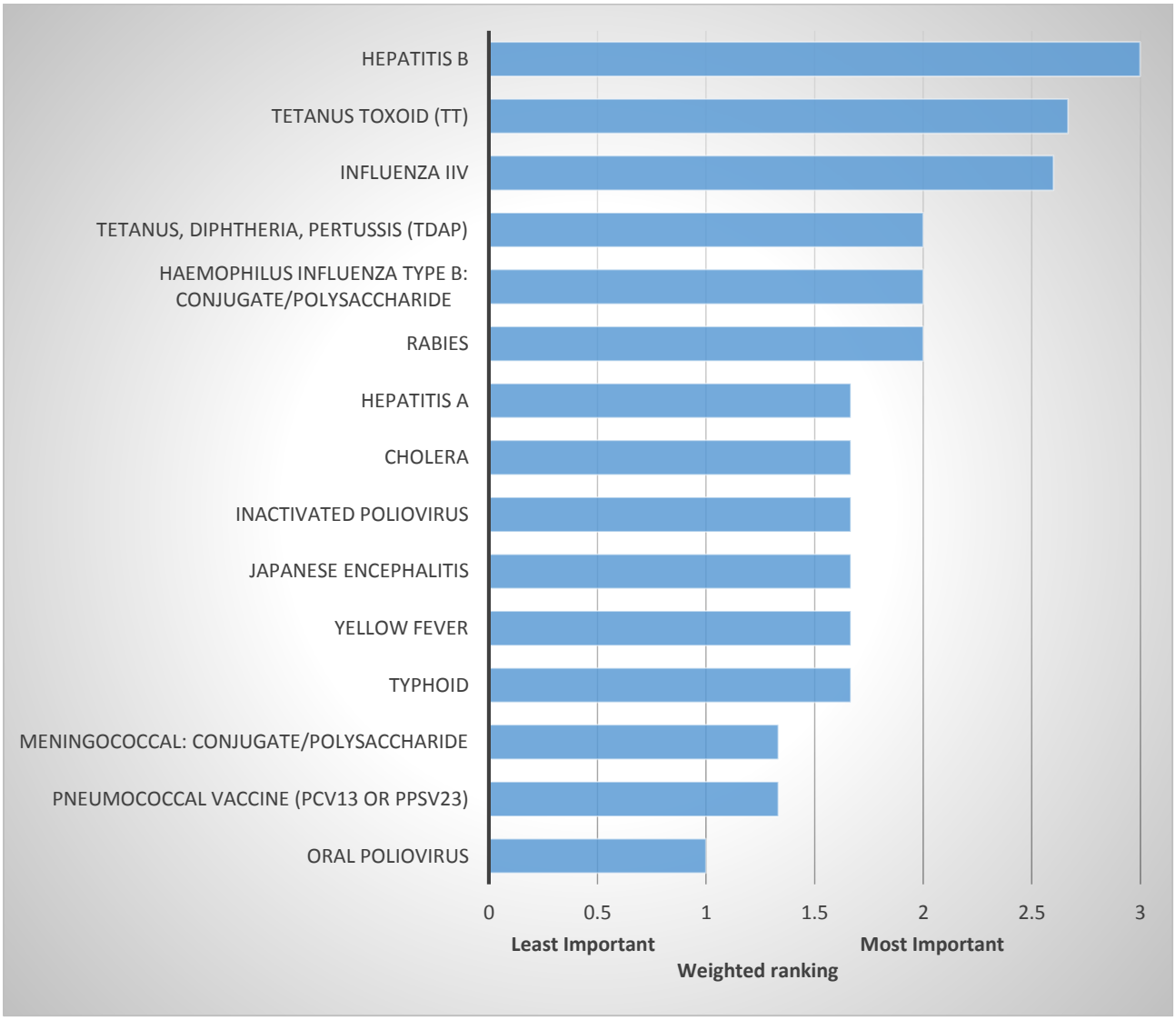


Figure 4. Countries' maternal immunization priorities for vaccines currently prequalified by the World Health Organization.
Note: IIV, inactivated influenza vaccine.

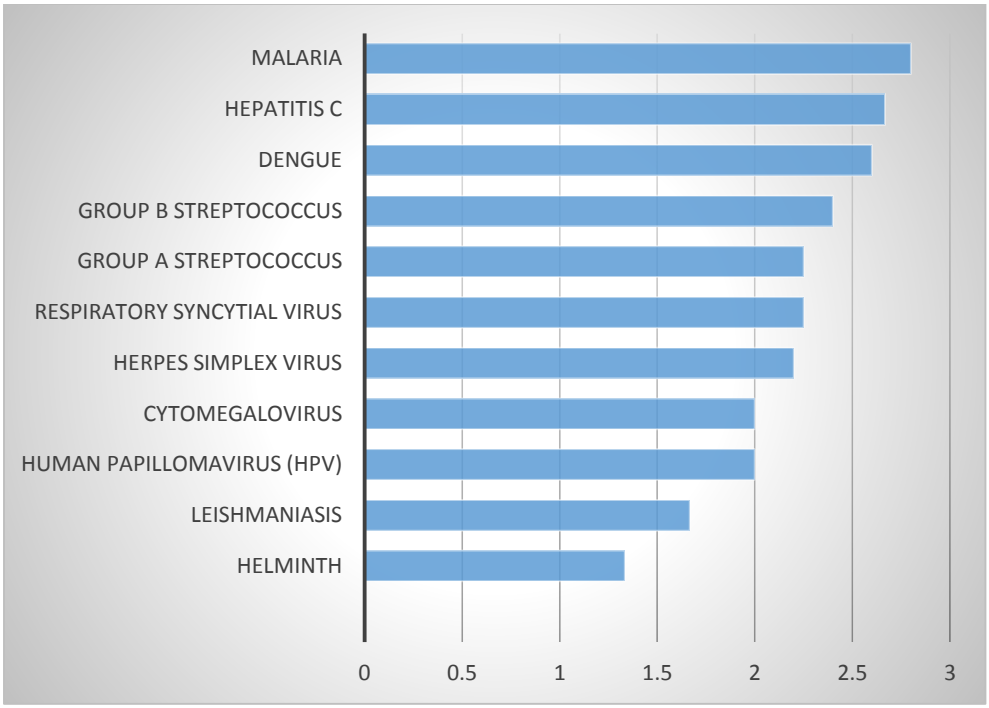


Figure 5. Countries' maternal immunization priorities for vaccines under development or not currently prequalified by the World Health Organization.[c]

Asked to justify their ranking of current and potential new vaccines for use in maternal immunization programs, most respondents cited the disease burden and epidemiology in their countries as the driving factors (6/9). Other reasons included possible funding streams and general benefits to pregnant women.

Discussion

The findings of the surveys have implications for country-level program planning in a number of areas, as discussed below.

Integrating maternal immunization into ANC services

Across respondents, the format and priorities for maternal immunization varied widely. Of 14 countries surveyed, 8 did not integrate their maternal immunization strategy into ANC services, as is widely recommended as the best practice for successful maternal immunization uptake. In addition, 5 countries had either no formal monitoring mechanism for maternal vaccination, or their monitoring mechanisms were intermittent. Each of these approaches is a recommended component of a successful immunization program and would be an effective step toward improving overall robustness of those countries' strategies.

[c] HPV vaccine was erroneously included in this survey question. HPV vaccine has WHO PQ. However, it is contraindicated for use in pregnancy and therefore should not have appeared in the survey. We have included the data here, and in the combined chart (Figure 6) below, as they reflect respondents' priorities.

Addressing key barriers and programmatic concerns

Key barriers identified through this survey focused on patient-centered issues, such as lack of access to services, low awareness of the value of vaccination during pregnancy, and low ANC participation. Integrating maternal immunization services into standard ANC services may help alleviate some of these barriers, while developing vaccine presentations that are suitable for community-based and home-based care may improve reach into populations with limited access to ANC services.

Addressing high-priority diseases with vaccine

Priorities identified by country-level respondents offered insights into differences between country- and global-level experts for addressing maternal and neonatal burden of disease (Table 5). While the top five high-priority diseases at the global level are tetanus, influenza, GBS, infections caused by RSV, and pertussis, at the country level these priorities shift to include hepatitis B rather than RSV, and they exclude GBS in favor of malaria, hepatitis C, and dengue among diseases without currently prequalified vaccines. However, in a subanalysis, weighted ranking of all responses for both categories combined reveals a surprising result: the weighted responses favor diseases without prequalified vaccines as higher priority for introduction, yielding a combined priority list very different from the current global stakeholders' agenda. In this analysis, only TT remains constant between country- and global-level priority lists. A complete list of combined priorities is presented in Figure 6.

Table 5. Top five vaccine choices for maternal immunization as communicated by global- and country-level experts. Vaccines include both those currently available and possible future vaccines.

Global experts	Country experts
TT*	**Hepatitis B***
IIV*	**Malaria**
GBS	**Hepatitis C**
RSV	**TT***
Pertussis*	**Dengue**

Currently available.
Note: GBS, group B streptococcus; IIV, inactivated influenza vaccine; RSV, respiratory syncytial virus; TT, tetanus toxoid.

A limitation of this analysis is that participants were not directly asked to rank prequalified and future vaccines on the same scale, as the comparison is limited by the varying stages of development of the different vaccines. The combined-priority ranking is obtained by combining the weighted rankings of both categories. A follow-on exercise exploring this line of inquiry by asking respondents to prioritize by disease category rather than by vaccine may offer a more robust analysis of this interesting discrepancy between country-level and global-level priorities.

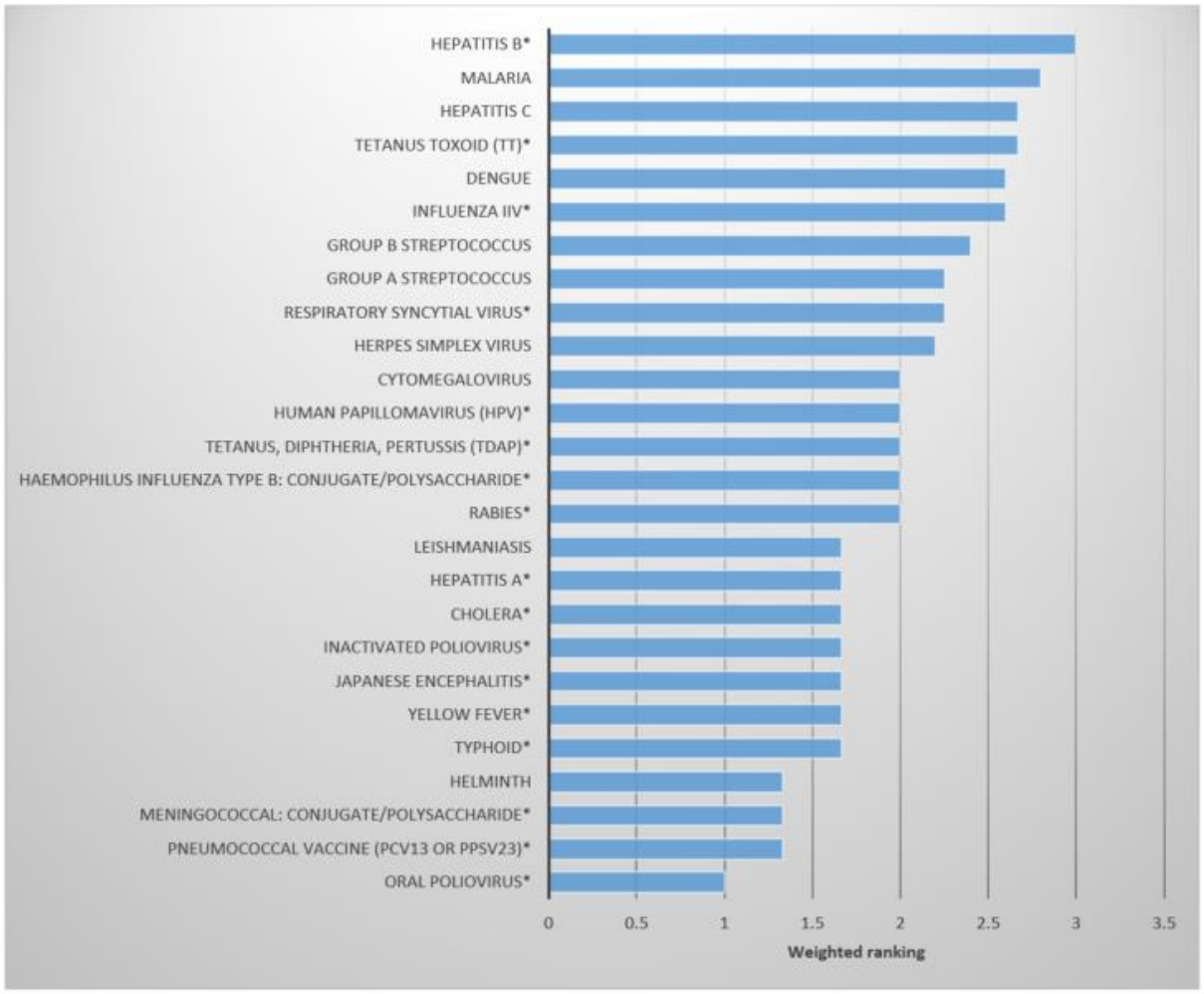


Figure 6. Combined maternal immunization priority vaccines listed by national stakeholders—currently prequalified and possible future vaccines (N = 14).
**Currently available vaccine.*

State of the market for high-priority vaccines for maternal immunizations

We used World Bank data to begin to estimate the demand for maternal vaccinations through 2025. Using population and birth rate data, we projected the number of births per year globally and in each of our target countries. Data on total live births were used as a proxy for total number of pregnant women who would receive maternal vaccine, based on the assumption that vaccination would occur during each pregnancy, regardless of order (i.e., a subsequent pregnancy requires the same vaccine doses as a first pregnancy). Because most doses of maternal vaccines are given in the third trimester, the number of stillborn and aborted pregnancies will marginally impact the calculation of vaccine demand. Likewise, multiple births may result in a marginal overestimation of demand.

Based on these calculations, we determined that the total number of live births—representing the total available market (TAM) for maternal vaccines from 2016 to 2025—is 1.37 billion. We then refined the TAM to account for less than 100 percent coverage of maternal vaccines by factoring in the coverage

rate for two or more doses of TT vaccine in pregnant women (TT2+), which, at 65 percent globally in 2014,[26] is the generally recognized indicator for coverage of maternal vaccination. We then calculated the average annual increase in TT2+ coverage from 2000 to 2013 to be an increase of 0.23 percent increase per year. Using these rates and assuming a single dose of vaccine per woman, we concluded that the likely demand for maternal vaccines from 2015 to 2025 will be at least 939 million courses of each vaccine included in global maternal immunization strategies. However, this projection will vary depending on the speed with which new vaccines are introduced into maternal immunization programs.

To estimate the potential revenue for a vaccine included in maternal immunization schedules, we looked at historic prices. Because prices for newer vaccines vary significantly from those that no longer have patent protection, we calculated this twice. Using a list of vaccines currently purchased by UNICEF, the first group of vaccines we considered were those that were released less than ten years ago (human papillomavirus [HPV], Japanese encephalitis, pneumococcal vaccines [PCV], and inactivated poliovirus vaccine [IPV]). For these, the average price was US dollar (USD) 3.94, with a high of USD 7.00 (PCVs) and a low of USD 0.42 (Japanese encephalitis). For vaccines that have been on the market and purchased by UNICEF for over ten years (diphtheria-tetanus, Tdap, hepatitis B, meningococcal, oral poliovirus, TT, and yellow fever vaccines), we calculated the average price to be USD 0.69, with a high of USD 2.50 (meningococcal) and a low of USD 0.09 (TT). Using these average prices combined with the total market calculation, we estimate a newer vaccine priced at USD 3.94/dose and released globally would generate approximately USD 3.7 billion in revenue between 2016 and 2025. Using the same rationale, an older vaccine priced at USD 0.69/dose would generate USD 647 million globally between 2016 and 2025.

Regulatory requirements

Vaccine candidates must satisfy regulatory requirements to ensure that products are safe, effective, and appropriate for target populations. For vaccines targeting diseases prevalent in LMICs, navigating local, regional, and international regulatory requirements at each stage can be challenging. Regulatory capacities of national regulatory authorities (NRAs) in LMICs can be limited, and guidance on vaccines for use in special high-risk populations like pregnant women can be vague or nonexistent, which can impede product development and launch. Thus, regulatory requirements can pose barriers to approval and implementation of maternal vaccinations.

Given that maternal vaccinations have the potential to provide benefits to the mother, fetus, and newborn, NRAs should take into account the impact of a vaccine candidate on each of these groups. Discussion on how to approach ethical and safety considerations for maternal vaccines is limited among NRAs in LMICs and is primarily led by the US Food and Drug Administration (FDA). Data demonstrating safety and effectiveness of vaccines for use in pregnancy are limited and largely generated in US and European populations. Product developers may face unique regulatory hurdles in countries with limited regulatory capacity and no experience licensing vaccines targeting pregnant women.

This section provides a summary of regulatory mechanisms and resources to support the development of vaccines in LMICs and vaccines paired with new packaging or delivery technologies. This section also explores the regulatory environment for maternal immunizations, including regulatory issues surrounding the coupling of maternal immunizations with new delivery technologies. The regulatory environments of the six countries of interest in this report are presented in Appendix 2 and Appendix 3.

Global regulatory stakeholders

Partnerships among a number of global-level stakeholders facilitate regulatory review and drive the pipeline of vaccines intended for LMICs. Collaboration among WHO, stringent regulatory authorities (SRAs), NRAs in LMICs, and regulatory harmonization initiatives helps ensure that new vaccines meet regulatory requirements for product approval and use.

Regulatory harmonization initiatives

Regional regulatory harmonization initiatives provide a mechanism for collaborating representatives from NRAs to harmonize regulatory requirements and undertake joint regulatory capacity-building. Primary regional regulatory harmonization initiatives include the African Medicines Regulatory Harmonization (AMRH) initiative, Asia-Pacific Economic Cooperation, Association of Southeast Asian Nations (ASEAN) Pharmaceutical Product Working Group, and the Pan American Network for Drug Regulatory Harmonization. Although they are not decision-making bodies, regulatory harmonization initiatives are platforms to engage with representatives of NRAs with common interests and to highlight vaccine candidates in the pipeline for regulators. Regulatory harmonization initiatives cooperate closely with WHO. For example, the AMRH's African Economic Community has conducted joint assessments with WHO for product registration.

WHO

Although WHO itself is not a regulatory authority, it facilitates regulatory approvals by establishing general standards, publishing international regulatory guidance documents, and strengthening regulatory capacity in LMICs through its network of country offices. This support is conducted in collaboration with NRAs, SRAs, donors, vaccine distributors, and product developers. WHO provides regulatory oversight through the PQ program, which ensures that global health products are of acceptable quality, safety, and efficacy. UNICEF and the Pan American Health Organization Revolving Fund procure vaccines for nearly all LMICs, and they rely on WHO PQ decisions when making purchases.[27]

The PQ program has separate teams that prequalify vaccines and medical devices and currently does not have a specific PQ procedure for products used for maternal immunization. There are three conditions that must be met for a vaccine to be eligible to apply for PQ:

1. The vaccine candidate is on WHO's high-priority vaccine list, which WHO updates every two years.[28]
2. The vaccine candidate is manufactured and licensed in a country with a "functional" NRA. WHO deems an NRA functional based on assessment benchmarks.[d]
3. The vaccine candidate meets programmatic suitability criteria in WHO's *Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification*. [29]

Additional guidelines for PQ of vaccine-coupled packaging or delivery technologies are outlined in *Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification*.[29]

WHO coordinates two additional mechanisms to help accelerate national registration of prequalified products. The first is joint dossier assessment with NRAs and the PQ team. PQ and NRA assessments are

[d] Countries that are functional and currently export prequalified vaccines: Australia, Belgium, Brazil, Bulgaria, Canada, China, Cuba, Denmark, France, Germany, India, Indonesia, Italy, Japan, the Netherlands, Korea, Russia, Senegal, Sweden, Thailand, the United Kingdom, and the United States.

conducted in parallel, resulting in products that are registered in-country soon after receiving PQ.[30] A more formalized procedure is collaborative registration, which allows manufacturers to request that WHO share its PQ assessment with participating NRAs supporting NRA decision-making on whether to license a product. WHO first piloted collaborative registration with the successful licensure of MenAfriVac®.

AVAREF

Coordinated by WHO, the African Vaccine Regulatory Forum (AVAREF) has been an important mechanism for building regulatory capacity of NRAs in Africa and conducting joint reviews of clinical trial protocols for vaccines. AVAREF is composed of 21 member countries[e] and serves as a platform for knowledge sharing among participating NRAs in Africa, SRAs, and WHO. AVAREF prioritizes vaccine candidates targeting malaria, tuberculosis, and HIV/AIDS, and other novel vaccines.[31] AVAREF's joint review process has been used successfully for clinical trial approval of MenAfriVac® and the malaria vaccine RTS,S. Most recently, AVAREF played a central role in coordinating a joint review of Ebola vaccine clinical trials.[32]

Stringent regulatory authorities

Stringent regulatory authorities (SRAs) are regulatory authorities that are members, observers, and associates of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.[33] This affiliation denotes that SRAs are mature regulatory authorities that enforce strict regulatory standards. SRAs such as the European Medicines Agency (EMA) and the FDA support the global regulatory environment by providing technical assistance to NRAs in LMICs and aiding the regulatory assessment of global health products.

General regulatory pathways

Vaccines

Regulatory strategy for a vaccine is influenced by many factors, including the target product profile, NRA functional status, and approval timelines. There are several regulatory pathways pursued for launching prequalified vaccines. The first pathway involves initial approval by the NRA of the country where a vaccine is manufactured. As previously noted, in order to be eligible for PQ, an NRA must be considered functional by WHO. Following PQ, the vaccine could be registered by individual NRAs in targeted LMICs. Alternatively, a vaccine could first receive SRA approval and undergo PQ review and registration by individual NRAs. The EMA and the FDA both offer regulatory assistance to expedite approval of products targeting diseases in LMICs and unmet medical needs. For example, the EMA's Article 58 process allows vaccine developers to receive a scientific opinion from the EMA on a vaccine candidate that will be exclusively used outside of the European Union. Article 58 is linked to the PQ process and has resulted in reduced timelines for NRA approval and PQ.[34]

Combination products

WHO's *Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification* document recommends the use of vaccine presentations that minimize potential errors in preparation and administration.[35] In some cases, vaccines are coupled with delivery devices to minimize use errors

[e] Botswana, Burkina Faso, Central African Republic, Republic of the Congo, Democratic Republic of the Congo, Equatorial Guinea, The Gambia, Ghana, Guinea, Kenya, Malawi, Mali, Mozambique, Niger, Nigeria, Senegal, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe.

and optimize the programmatic suitability of the vaccine presentation. These are considered combination products and include delivery systems like the Uniject™ cPAD, prefilled hollow microneedle devices, blow-fill-seal prefilled ampoules, dual-chamber reconstitution devices, and MAPs. The regulatory pathway for approval of a vaccine coupled with a new delivery technology or a vaccine presented with a different formulation, packaging, or stabilization profile depends on the nature of the product. Recently, WHO and PATH established a dedicated working group for delivery technologies under the WHO Vaccine Presentation and Packaging Advisory Group (VPPAG) in order to provide a route for vaccine manufacturers and technology developers to obtain design, technical, and programmatic feedback on technologies in development.[f] [36]

Combining a vaccine with a new type of primary vaccine packaging—packaging that directly holds a vaccine—is considered a major change by the FDA, the EMA, and WHO and would be required to submit to the regulatory process for combination products. Combination products are regulated based on the component that contributes to the primary mode of action (PMOA) to achieve the desired therapeutic effect. The PMOA determines which regulatory center has primary jurisdiction over the combination product, and the primary review center would consult with additional review centers for supplemental guidance. For a biologic-device combination where the PMOA is pharmacological, the combination product would be regulated in the United States by the FDA's Center for Biologics Evaluation and Research (CBER) and in the European Union by the EMA. If the PMOA of a biologic-device combination is through physical means, the combination product would be regulated in the United States by the FDA's Center for Devices and Radiological Health (CDRH) and in the European Union by a notified body for Conformité Européenne (CE) marking. The FDA considers a different presentation for vaccines that are already marketed to be a major change. A Prior Approval Supplement must be submitted for a vaccine to be approved in a new presentation.[37] Technologies like MAPs, which involve a new route of delivery and vaccine formulation, may be subject to additional data requirements for regulatory approval, including stability, depth of penetration, and skin recovery studies.

Stand-alone vaccine delivery devices

It is important to note that not all new delivery technologies to be used with vaccines are regulated as combination products. Products that are freestanding and are to be marketed as a device that can be used with more than one vaccine or pharmaceutical product—such as field-filled hollow microneedle delivery devices and relatively simple technologies such as bundling clips for the vaccine and diluent vials and/or ampoules—are regulated as stand-alone medical devices. New primary vaccine packaging could impact the quality, safety, or efficacy of a vaccine, so the FDA, the EMA, and WHO would expect to see supporting data to change primary (and sometimes secondary) vaccine packaging of a currently marketed vaccine. These products would be regulated in the United States by CDRH and in the European Union by a notified body for CE marking. However, depending on the NRA, some products that are freestanding—like DSJIs—can be regulated as combination products. The FDA requires that each vaccine be relabeled for use with a particular DSJI.[38]

Secondary and tertiary packaging

Vaccines suitable for PQ must be packaged in materials that can be disposed of through standard means in the field, and environmental impact of waste disposal should be minimized. Changes to secondary

[f] The VPPAG website can be found at: http://www.who.int/immunization/policy/committees/vppag/en/index2.html.

and tertiary packaging, which would include shipping containers, generally do not require additional regulatory approval.

Overview of maternal immunization regulatory environment

Maternal vaccines present unique regulatory challenges because safety and efficacy must be considered for the mother, fetus, and newborn. Currently, vaccines administered through maternal immunization programs are widely administered off-label and have not been officially approved for use in pregnant women. In the United States alone, there are no vaccines specifically licensed for use during pregnancy.[39] Although a vaccine may not be approved for a specific population, off-label use is permitted if a vaccine would provide benefits that would outweigh potential risks. Historically, pregnant women have not been included in vaccine labels because pregnant women are omitted from clinical trials. Regulatory policy specifically addressing maternal vaccine development is limited among SRAs and nonexistent among NRAs of LMICs. Although there are limited data on reproductive toxic effects of approved vaccines, the preclinical and clinical study for a maternal vaccine candidate must be carefully designed to take into account ethical considerations and minimize the possibility of adverse effects.

The FDA has been at the forefront of discussion on regulatory approaches to maternal vaccine development. In 2006, the FDA published *Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications*.[40] According to the guidance, unless a vaccine candidate is indicated for maternal immunization, product developers do not conduct clinical studies in pregnant women. Pregnant women are generally ineligible to participate during any clinical trial; however, federal regulations state that pregnant women can participate in clinical research to meet the mother's health needs, regardless of the risk to the fetus and newborn.[41] Similarly, US federal regulations permit clinical research with a fetus as the subject if the research aims to meet the health needs of the fetus and risk to the fetus is minimized. According to the guidance, the FDA recommends that before a clinical trial is initiated with pregnant women, vaccine developers supply data from nonclinical developmental toxicity studies.

According to Marion Gruber, director of the FDA's CBER, vaccines that are to be approved specifically for pregnant women would require safety and efficacy data in pregnant women. This includes vaccines that are already recommended by policymakers for use in pregnant women (influenza, Tdap) and new vaccines (RSV, GBS).[17] Clinical trials would need to monitor for potential vaccine effects on pregnancy outcomes and perinatal/postnatal events. Correlation of adverse events with vaccination of pregnant women may be difficult to establish, given general pregnancy risks.[42] Endpoints used to assess clinical efficacy would be based on whether the vaccine would be indicated for the prevention of a disease in the mother and/or infant.

At a WHO consultation on RSV vaccine development in 2015, a representative from CBER outlined a clinical development plan that would support the FDA's licensure of RSV vaccines for pregnant women. Phase I and Phase II studies would first be conducted in nonpregnant women of childbearing potential to determine safety and immunogenicity. Following positive results from these studies and a preclinical reproductive toxicity study, the vaccine candidate could be tested in a Phase I study with low-risk pregnant women to determine safety. Phase II and Phase III studies could then be conducted in pregnant women to determine safety, immunogenicity, and efficacy. These studies would support licensure of the RSV vaccine in pregnant women, and sponsors would be expected to conduct postlicensure studies in pregnant women. [43]

In the United States, in order for a vaccine to be relabeled with an indication for pregnancy, vaccine developers would have to conduct clinical trials to demonstrate safety and efficacy in pregnant women. The FDA updated its pregnancy and lactation labeling rules in June 2015, whereby manufacturers can submit a short description of risk and benefits of administering a product to pregnant women. This does not have an impact on the approved indication for a licensed vaccine; rather, it is intended to inform a health professional in advising whether the vaccine could be used during pregnancy.[Error! Bookmark not defined.]

The United Nations currently purchases prequalified vaccines against tetanus and influenza for maternal immunization. In the case of prequalified influenza vaccines, the labeling generally includes a precautionary warning that the vaccine should be administered to pregnant women only after the mother consults with a health care professional on benefits and risks to the mother and fetus.[44] Prequalified TT vaccines do include immunization during pregnancy on their labels.[45] If a vaccine is currently prequalified but not approved for use in pregnant women, a product sponsor must submit additional data to WHO to support a label change. The product sponsor must also receive labeling change approval from the NRA, which can be pursued in parallel. The WHO PQ team can process a labeling change in approximately 90 days.[45]

Pairing maternal immunizations with new delivery and packaging technologies

Although there is limited discussion of specific regulatory requirements for the approval of vaccine-coupled technologies for maternal immunization, there are several vaccine technology pairings that are especially relevant to the maternal immunization context.

Approval of a vaccine-device combination product specifically licensed for pregnant women would likely require that the vaccine is approved for use in pregnant women. As stated above, vaccine developers would be expected to provide safety and efficacy data in pregnant women. In the United States, for a vaccine-device where the PMOA is pharmacological—which would include prefilled syringes and MAPs intended for maternal immunization programs—the Center for Drug Evaluation and Research would provide CBER supplemental support to determine any additional regulatory requirements on the device component of the product. MAP technology has been evaluated for delivery of many high-priority maternal vaccines, including TT and influenza, which are of high priority to maternal immunization campaigns. MAPs are currently in early stages of development for TT and influenza vaccine administration, with hopes that this pairing could be used in the maternal immunization context.[46] Given the priority for reducing the prevalence of malaria among pregnant women, it is worth highlighting a future possibility of delivering a malaria vaccine with an ID delivery device. If malaria vaccine is licensed in the future for booster doses delivered intradermally, marketing a freestanding ID delivery device—such as a field-filled, hollow, or mini-needle microneedle device or the ID adapter—would require regulatory clearance of the device in the United States by CDRH and in the European Union by a notified body for CE marking. These regulatory bodies would be responsible for determining any additional regulatory requirements for the use of these devices in the maternal immunization context.

Conclusions

Maternal immunization can protect both mothers and neonates from infections such as tetanus and influenza, but more evidence is needed on the safety and efficacy of other vaccines that could be used for pregnant women. Data are also needed on the root causes of neonatal deaths reported as prematurity or sepsis, which can result from diseases such as influenza, malaria, pneumonia, or

meningitis. These data can give global organizations and national health systems the ability to proceed with recommending more vaccines during pregnancy.

Despite the growing evidence for the benefits of maternal immunization, few LMICs provide this service. A survey of 14 countries showed that barriers to vaccinating pregnant women include personal obstacles such as patient lack of awareness, low ANC participation, concern regarding fetal safety, cost, and cultural bias. Programmatic barriers included inadequate reach of the health system to marginal populations and lack of integration of maternal immunization into existing programs. National stakeholders ranked increasing demand among pregnant women, setting maternal immunization policy, and training health care providers as top programmatic priorities.

Priorities for specific vaccines—either available or not yet developed—that should be provided to pregnant women differed between global and national stakeholders. The former recommends vaccines for **tetanus**, **influenza**, GBS, infections caused by RSV, and **pertussis**; at the country level, these priorities are **hepatitis B**, malaria, hepatitis C, **tetanus**, and dengue (bold font indicates those currently available). Clearly it will be necessary for all parties to analyze reasons for these differences and come to agreements on priorities.

In addition to the problems presented by personal and programmatic barriers and the lack of agreement on vaccines to prioritize for maternal immunization, regulatory requirements are another hurdle once vaccines are ready for use. The regulatory capacity of NRAs in LMICs is generally limited, and guidance on labeling vaccines for use in special high-risk populations such as pregnant women can be vague or nonexistent, impeding product development, approval, and launch. Guidance from WHO and collaboration of countries via regional regulatory harmonization initiatives and other mechanisms will support these efforts.

With maternal immunization gaining momentum as a global health priority, new research into the potential safety, efficacy, and cost-effectiveness of available vaccines will be needed to encourage LMICs to invest in strengthening their maternal immunization strategies. When other vaccines become available, such as those for RSV, malaria, or GBS, these countries will need help to navigate regulatory approval processes and launch vaccines for use.

New and alternative packaging and delivery technologies have the potential to improve access to these new products. These may include primary containers such as blow-fill-seal ampoules or integrated reconstitution vials and syringes; delivery devices combined with existing vaccine presentations, such as prefilled reconstitution syringes or DSJIs; delivery devices combined with new routes of delivery for vaccines, such as ID injection adapters for needle and syringe injections; or delivery methods requiring new formulation, such as MAPs for skin vaccination (Figure 7). An in-depth needs assessment in target

scenarios of use for maternal vaccines will help align the optimal packaging and delivery technology configurations with new and existing vaccines for maternal immunization.

Photos: PATH and Georgia Tech (far right)

Figure 7. DSJIs, integrated reconstitution devices, ID injection adapters, and MAPs are examples of alternative packaging and delivery options to address barriers to maternal immunization coverage.

Appendix 1: Country maternal immunization priorities survey

Participant background and role

Through this survey, we aim to determine the current state of the market for maternal immunization and assess stakeholder requirements. This information will be used to characterize the priorities for maternal immunization implementation and program planning in your country. Thank you for your participation.

1. Name

2. Country

3. What is your current position?

4. At what institution do you work?

5. For how many years have you been working in this field?

Maternal immunization policies and programs

6. Does your country currently have a dedicated maternal vaccination policy or program?

- ◯ Yes
- ◯ No

Country policies and programs

7. About how long has this policy been in place?

- ◯ Less than 5 years
- ◯ More than 5 years

8. What vaccines are included in this policy and what are the estimated rates of coverage?

	Vaccine status in country	Estimated coverage
Influenza IIV		
Tetanus, diphtheria, pertussis (Tdap)		
Tetanus toxoid (TT)		
Pneumococcal vaccine (PCV13 or PPSV23)		
Meningococcal: conjugate/polysaccharide		
Haemophilus influenza type B: conjugate/polysaccharide		
Inactivated poliovirus		
Typhoid		
Cholera		
Hepatitis A		
Hepatitis B		
Rabies		
Japanese encephalitis		
Yellow fever		
Oral poliovirus		

Other (please specify).

9. What are some of the challenges for increasing coverage of maternal vaccines?

Barriers to greater access and uptake of maternal immunization.

10. What are the biggest barriers to greater coverage of maternal vaccines?

- [ ] Health system barriers: service delivery (coverage, surveillance and reporting, communication)
- [ ] Health system barriers: logistics (cold chain capacity, vaccine stock management, transport management)
- [ ] Health system barriers: health planning and management (financing and human resources)
- [ ] Health care provider barriers: knowledge, unaware of immunization benefits
- [ ] Health care provider barriers: low antenatal care (ANC) attendance rates
- [ ] Health care provider barriers: logistics (storage and cold chain, vaccine stock)
- [ ] Patient barriers: knowledge (education and social mobilization)
- [ ] Patient barriers: accessibility (outreach and socioeconomic status)
- [ ] Patient barriers: health decision-making skills (age, parity, culture)

Other (please specify).

11. Which barriers most effect greater maternal immunization access and uptake in your country?

	No effect		Some effect		Significant effect
Health system barriers: service delivery (coverage, surveillance and reporting, communication)	○	○	○	○	○
Health system barriers: logistics (cold chain capacity, vaccine stock management, transport management)	○	○	○	○	○
Health system barriers: health planning and management (financing and human resources)	○	○	○	○	○
Health care provider barriers: knowledge, unaware of immunization benefits	○	○	○	○	○
Health care provider barriers: low ANC attendance rates	○	○	○	○	○
Health care provider barriers: logistics (storage and cold chain, vaccine stock)	○	○	○	○	○
Patient barriers: knowledge (education and social mobilization)	○	○	○	○	○
Patient barriers: accessibility (outreach and socioeconomic status)	○	○	○	○	○
Patient barriers: health decision-making skills (age, parity, culture)	○	○	○	○	○

Other (please specify).

Funding Maternal Immunization

12. Compared to other health issues, how does funding for maternal immunization rank when allocating budget?

- ○ A high priority
- ○ A medium priority
- ○ A low priority

13. Where does the funding come from for the procurement and distribution of maternal vaccines?

14. Is maternal immunization integrated into a government program such as the Expanded Programme on Immunization (EPI) or maternal and child health (MCH)? If not, who is responsible for materna vaccine supply and monitoring?

15. If yes, with which program is it integrated?

- ◯ EPI
- ◯ MCH

Other (please specify)

Maternal immunization priorities

16. Please rank in order of importance the priority areas of focus for the next 5 years for maternal immunization in your country with 1 being the most important and 7 being the least important.

- Setting maternal immunization policy
- Introducing new vaccines
- Expanding coverage of specific vaccines
- Expanding coverage within specific populations or geographic regions
- Strengthening the vaccine supply chain
- Training maternal health providers
- Increasing demand for immunizations for women during pregnancy

17. What are other priorities for maternal immunization in your country?

18. Which currently available vaccines are most important for maternal immunization in your country?

	Importance
Influenza IIV	
Tetanus, diphtheria, pertussis (Tdap)	
Tetanus toxoid (TT)	
Pneumococcal vaccine (PCV13 or PPSV23)	
Meningococcal: conjugate/polysaccharide	
Haemophilus influenza type B: conjugate/polysaccharide	
Inactivated poliovirus	
Typhoid	
Cholera	
Hepatitis A	
Hepatitis B	
Rabies	
Japanese encephalitis	
Yellow fever	
Oral poliovirus	

Other (please specify).

19. Which vaccines under investigation or under development could be important for maternal immunization in the future in your country?

	Importance
Human papillomavirus (HPV)	
Herpes simplex virus	
Cytomegalovirus	
Respiratory syncytial virus	
Group A streptococcus	
Group B streptococcus	
Malaria	
Dengue	
Hepatitis C	
Leishmaniasis	
Helminth	

Other (please specify).

20. Why did you prioritize the vaccines as such?

Vaccine procurement and supply chain management

21. What facilities provide maternal immunization services in the public health system?

22. What kinds of providers are primarily responsible for giving maternal vaccines?

23. Is this different within the private health system and if yes, how so?

24. How does your country monitor vaccines that are given to pregnant women?

Vaccine delivery scenarios

25. What proportion of women seek care from providers during pregnancy?

26. In general, do health care providers recommend vaccination to pregnant women or do pregnant women request vaccination?

27. What are common reasons that women and their families may decide not to get vaccinated during pregnancy? Indicate all that apply.

- [ ] Concerns regarding fetal safety or adverse pregnancy outcomes
- [ ] Vaccination is not recommended by health care provider
- [ ] Women are not aware of national recommendations
- [ ] Going for vaccination is inconvenient
- [ ] Cost

Other (please specify).

Thank you for your participation!

28. What else is important to know about maternal immunizations in your country?

29. Are there others who we should contact about maternal immunizations in your country?

Please feel free to share this survey link with them (https://www.surveymonkey.com/r/matimm) or provide their contact details below. (We will not share this information).

Name	
Institution	
Email address	
Name	
Institution	
Email address	

30. May we contact you if we have follow-up questions?

- ◯ Yes
- ◯ No

31. Email address

Appendix 2: Country-specific summaries

Kenya

Image: WHO

Program status

Kenya's maternal immunization strategy is limited to tetanus toxoid (TT) vaccination. The elimination of TT among pregnant women and neonates is included in the national health strategic plan, and there is a disease-specific reference manual that focuses on TT vaccination in antenatal care (ANC) settings. Kenya's TT-specific maternal immunization strategy is a two-dose schedule: two doses during the first pregnancy, and one dose during each subsequent pregnancy through the fourth pregnancy, after which no further vaccination is recommended.

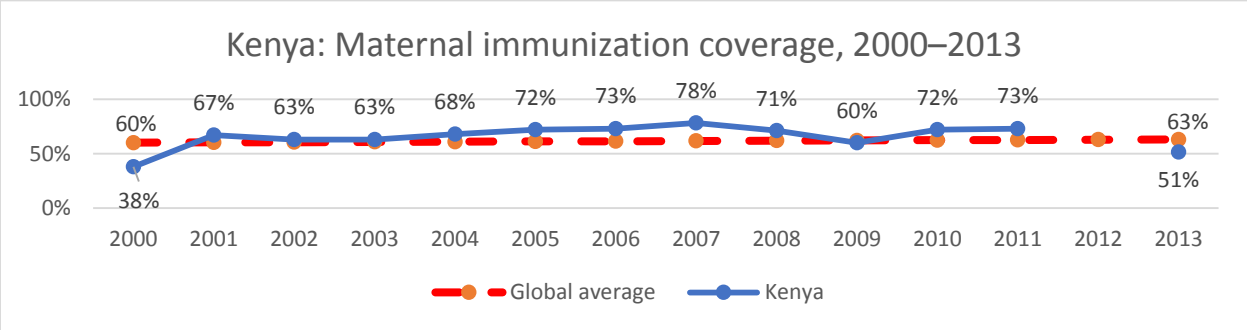
Programmatic priorities include increasing demand for immunizations among women during pregnancy, training maternal health providers to deliver vaccines, and integrating maternal immunizations with other health programs.

High-priority vaccines

Hepatitis A and B, along with yellow fever, are viewed as the most important currently available vaccines for inclusion in a maternal immunization strategy in Kenya. Among vaccines with possible application in maternal immunization, HPV, herpes simplex virus, Group B streptococcus, malaria, and hepatitis C are of greatest interest.

Maternal immunization coverage

As of 2013, Kenyan maternal immunization coverage was at 51 percent, below the global average. This rate is significantly lower than previous years and not representative of Kenya's historically positive trend toward immunization coverage in excess of global averages. While data were not available in 2012, two possible explanations for the dip in coverage in 2013 are vaccine shortages and an unfounded antivaccine campaign initiated by a subset of religious leaders.



Regulatory environment

The primary regulatory authority of Kenya is the Pharmacy and Poisons Board (PPB). While it is not considered a functional regulatory authority by WHO, in 2014, the New Partnership for Africa's Development designated the PPB as a Regional Centre of Regulatory Excellence in Pharmacovigilance in Africa. As a center of excellence, the PPB helps provide regulatory training in pharmacovigilance to other countries in Africa. Kenya is highly active in the African Medicines Regulatory Harmonization (AMRH)

initiative. There are no foreseeable major changes in the country's regulatory environment in the coming years. See Appendix 3: Regulatory table for further details.

Senegal

Image: WHO

Program status

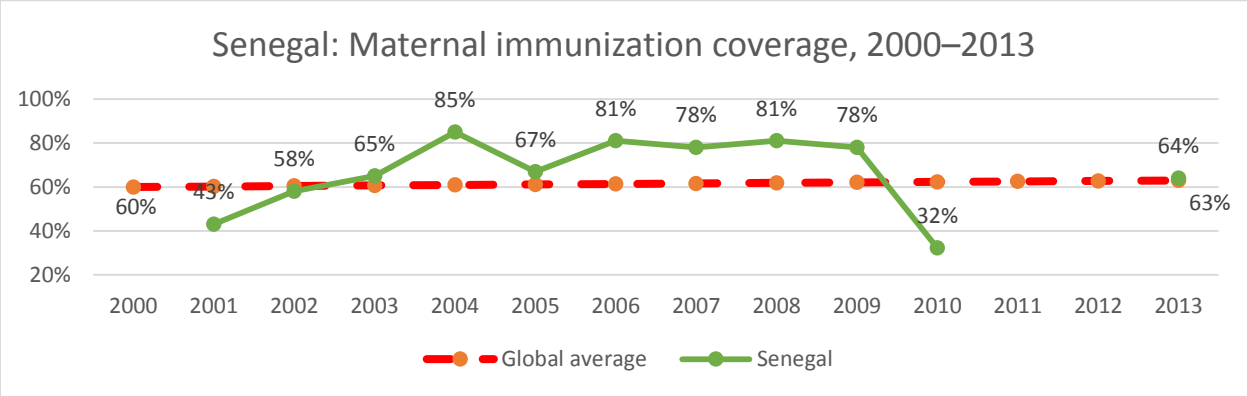
Senegal has achieved elimination of tetanus and includes maintaining eliminated status within its objectives for the EPI.[47] The Senegal EPI Comprehensive Multiyear Plan list includes reaching 90% coverage for TT2+. No other maternal vaccines are included in the multiyear plan.[48]

High-priority vaccines

No Senegalese respondent completed the survey to indicate which vaccines would be a priority for introduction into a maternal immunization strategy in Senegal. Given that the timing of the survey coincided with the Ebola outbreak in West Africa, the absence of response is likely indicative of other immediate priorities within the Senegalese Ministry of Health.

Maternal immunization coverage

Senegal achieved considerable success with maternal tetanus coverage between 2001 and 2004, with some sustained losses in the next five years. Following a period without data, 2013 shows a significant drop in maternal tetanus coverage from the high point in 2004—21 percentage points. The reasons for this are unclear and require further exploration.



Regulatory environment

The Ministry of Health and Prevention oversees pharmaceutical regulation in Senegal. The national regulatory authority (NRA) is considered functional by WHO. Senegal manufactures one prequalified vaccine—yellow fever vaccine—and is the only country in Africa that manufactures a prequalified vaccine. Senegal is active in regulatory harmonization initiatives in West Africa through the West Africa Health Organization of the Economic Community of West African States. There are no foreseeable major changes in the country's regulatory environment in the coming years.

South Africa

Program status

Image: WHO

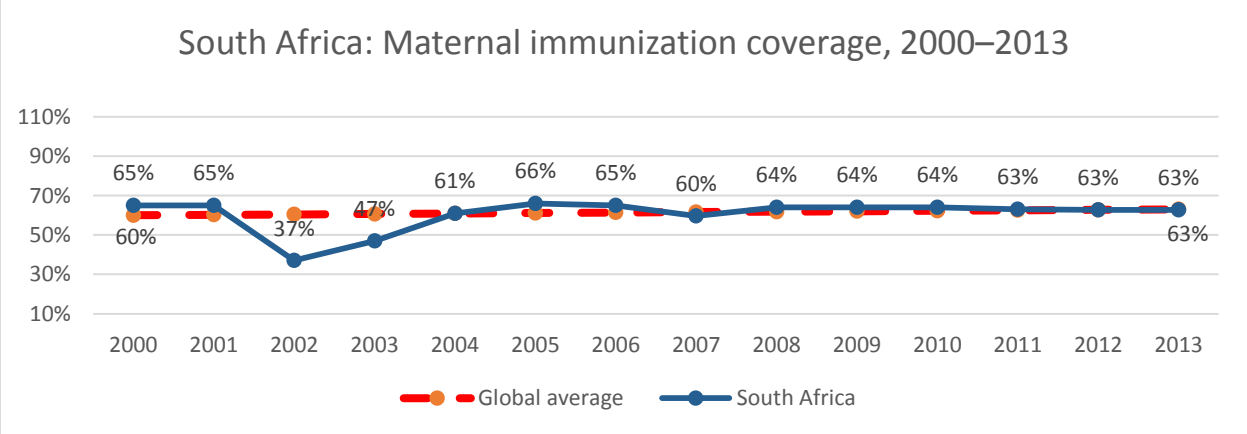
The maternal immunization program of South Africa has achieved an estimated TT2+ vaccine coverage of between 40 percent and 60 percent. However, maternal immunization is not effectively monitored, so there are insufficient data regarding rates of coverage and barriers to uptake. Maternal vaccine supply is integrated into maternal child health systems and is considered to be a high funding priority.

Increasing demand and updating maternal immunization policy are considered the top priorities for the maternal immunization program. In particular, the program focuses on addressing demand-related barriers, such as clients' concerns regarding fetal safety or adverse pregnancy outcomes.

High-priority vaccines

Currently, only TT is a high-priority vaccine. Efforts are focused on expanding coverage and addressing barriers to uptake of TT vaccine.

Maternal immunization coverage



Regulatory environment

The NRA of South Africa is the Medicines Control Council (MCC); however, WHO has not conducted a review to assess whether it is functional. Currently, vaccines are manufactured in South Africa primarily for the domestic market, and some are exported to Mozambique, Swaziland, and Namibia.[49]

In recent years, South Africa has been planning to replace the MCC with a new regulatory body, the South African Health Products Regulatory Agency. This agency would regulate medical devices and diagnostics, which are currently unregulated, and would also have its own dedicated staff, significantly enhancing South Africa's regulatory capacity, given that the MCC currently relies on part-time academics and medical professionals.

Vietnam

Program status

Vietnam's maternal immunization is more than five years old and has achieved greater than 80 percent coverage of TT2+, which is recommended and free. Patient factors such as health decision-making skills are identified as the primary barriers to greater coverage of maternal immunization. Increasing demand for immunizations for women during pregnancy and strengthening the vaccine supply chain are the top priorities for the Vietnam maternal immunization program.

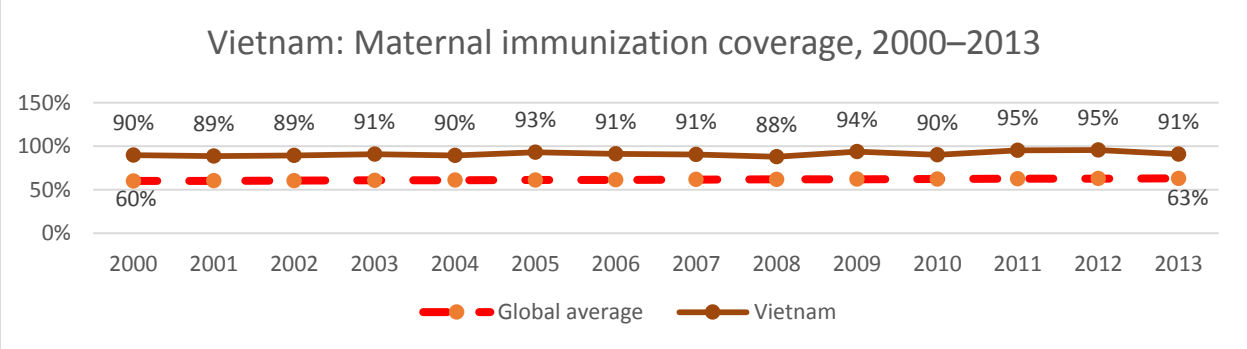
Image: WHO

High-priority vaccines

Among vaccines that are currently available, Hib, TT, IPV, hepatitis B, and Japanese encephalitis vaccines are of greatest interest for inclusion in the maternal immunization program. Vaccines for malaria and dengue have the greatest appeal among vaccines that are still in development.

Maternal immunization coverage

The consistently high coverage levels may be due in part to the country's ability to produce vaccines domestically.



Regulatory environment

The Drug Administration of Vietnam provides regulatory oversight of Vietnam's pharmaceutical industry. Manufacturers in Vietnam produce nearly all EPI vaccines for domestic use. Partnerships with other countries and vaccine manufacturers have led to significant technology transfer, resulting in local production of hepatitis B, Japanese encephalitis, cholera, rabies, and typhoid vaccines. In June 2015, WHO awarded the Drug Administration of Vietnam with functional status. It is anticipated that the first Vietnam vaccine could be prequalified in one to two years.[50] Vietnam is involved with the ASEAN Pharmaceutical Product Working Group and accepts the ASEAN Common Technical Dossier format for product registration.

India

Image: WHO

Program status

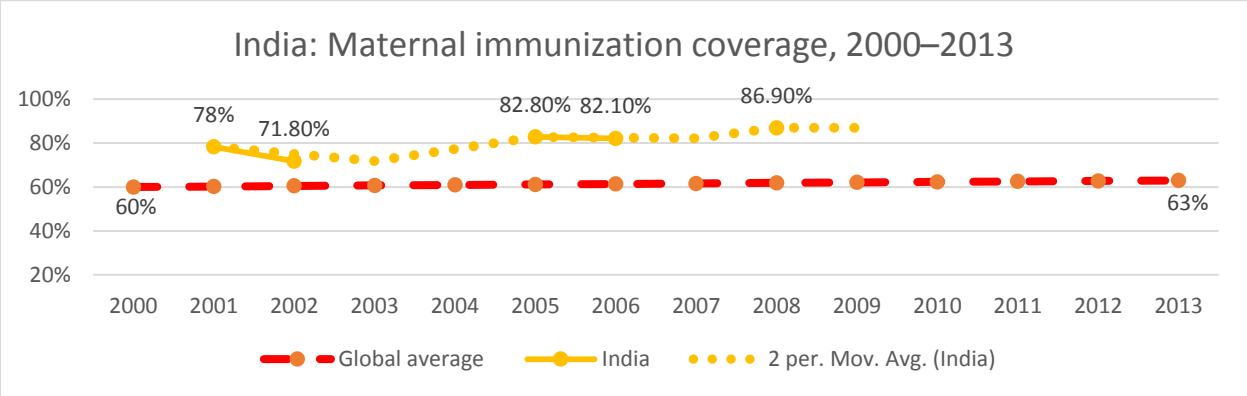
The Indian maternal immunization program has been in place for more than five years and has achieved an estimated TT vaccine coverage of between 60 percent and 80 percent. Maternal vaccine procurement and distribution are integrated into maternal and child health strategy in India. Health systems factors that were identified as the greatest barriers to expanding coverage of maternal immunizations included logistical issues such as cold chain capacity and vaccine stock management. Increasing demand for immunizations among women during pregnancy is the highest priority within India's maternal immunization program.

High-priority vaccines

Among currently available vaccines, TT, hepatitis B, and HPV are viewed as high-priority vaccines for the Indian maternal immunization program. The high rate of cervical cancer was cited as the reason for including HPV as a priority. No other vaccines were identified as high priority.

Maternal immunization coverage

The available data on India's maternal immunization coverage indicate a high coverage of maternal TT vaccination compared with the global average; however, the WHO/UNICEF coverage survey data for India have not been reported for maternal tetanus vaccine since 2008.



Regulatory environment

The Central Drug Standard Control Organization (CDSCO) is the primary regulatory body in India responsible for regulating vaccines. Regulatory oversight is divided among national and state offices. The Drugs and Cosmetics Act of 1940 outlines India's regulatory framework. CDSCO is a functional regulatory authority and the largest supplier of vaccines among LMICs.[51] Many vaccines produced in India are prequalified, and nearly one-third of vaccines purchased for global procurement are manufactured there.[52]

Due to understaffing and limited resources, it has been challenging for CDSCO to meet the regulatory demands of India's large vaccine industry. Strains on the system have prompted significant delays in regulatory review timelines for vaccine developers. To address this, CDSCO has tried to increase staffing

in order to support the regulatory authority.[53] In 2015, CDSCO introduced a "just in time" program, which expedites marketing approval of products developed in India. Timelines for approval under this program have been reduced to approximately a month—a considerable reduction from the three to six months normally required. Given India's role in the global vaccine supply, there has also been concentrated effort by WHO and the US FDA to provide technical assistance to support CDSCO. In terms of upcoming regulatory policy changes, amendments to the Drugs and Cosmetics Act have been pending for the past year. If approved, the amendments would formalize the regulation of medical devices in India, which could affect eventual approval of delivery devices for vaccines, including those for maternal immunizations.

China

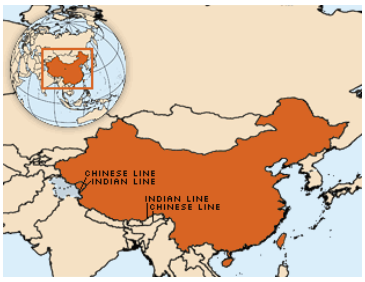


Image: WHO

Program status

China's maternal immunization policy recommends and provides free of charge tetanus toxoid, diphtheria, and acellular pertussis (Tdap); meningococcal; hepatitis A and B; Japanese encephalitis; and oral poliovirus vaccines. Maternal immunization is considered a high funding priority and is integrated into the EPI. In particular, expanding the maternal immunization policy and training health care providers are high priorities. Barriers that prevent improved access to and uptake of maternal immunization include low ANC attendance rates and patient-related barriers, including knowledge and health decision-making skills. Concerns regarding fetal safety or adverse pregnancy outcomes may cause women to opt out of maternal immunization. In China, 26 percent of neonatal deaths are attributed to "other conditions," which could account for the lower than average attribution toward infectious diseases.

Program priorities

Influenza, Tdap, TT, hepatitis B, and rabies are considered the most important diseases with currently available vaccines for maternal immunization, while herpes simplex virus, cytomegalovirus, dengue, and hepatitis C are the most important new or potential vaccines.

Gaps in maternal immunization coverage

Data on coverage rates specific to maternal immunization were not available from the main WHO database and are sparse within peer-reviewed literature. ANC coverage rates reported in the literature vary widely by source and region within China, ranging between as high as 94 percent access and as low as 20 percent access.[54,55]

Regulatory environment

The NRA of China is the China Food and Drug Administration (CFDA). In 2014, WHO designated the CFDA as a functional regulatory authority. The CFDA has approved more than 300 vaccines manufactured by Chinese pharmaceutical companies, which produce nearly all routine vaccines. China currently manufactures two prequalified vaccines—a Japanese encephalitis vaccine manufactured by Chengdu Institute of Biological Products and a flu vaccine manufactured by Hualan Biological Engineering.[56] Because of CFDA's functional status and prequalification of two vaccines, Chinese manufacturers have great interest in applying for prequalification and producing vaccines for global procurement.

Appendix 3: Regulatory table

Country	NRA	Recognized as functional by WHO	Official timeline for vaccine clinical trial approval	Official timeline for vaccine licensure approval	Collaborative registration participant	Export prequalified vaccines	Participation in regulatory harmonization initiatives and regulatory collaboration	Anticipated regulatory environment changes
China	China Food and Drug Administration	Yes	155 days[g]	90 days	No	Yes	APEC	Increased focus on getting more products prequalified.
India	Central Drug Standard Control Organization	Yes	180 days[h]	270 days	No	Yes		Approval of amendments to the Drugs and Cosmetics Act, which would create a regulatory framework for medical devices.
Kenya	Pharmacy and Poisons Board	No	30 days	90 days[i]	Yes	No	AMRH, AVAREF	
Senegal	Ministry of Health and Prevention	No	Unavailable	Unavailable	Yes	No	AMRH, AVAREF	
South Africa	Medicines Control Council	No	12 weeks (minimum)	Unavailable	Yes	No	AMRH, AVAREF	In the process of transitioning to a new regulatory authority, which would create a regulatory framework for medical devices.
Vietnam	Drug Administration of Vietnam	Yes	90 days	Within 6 months	No	No	ASEAN PPWG	PQ of first vaccine in the next one to two years.

Note: AMRH, African Medicines Regulatory Harmonization; APEC, Asia-Pacific Economic Cooperation; ASEAN, Association of Southeast Asian Nations; AVAREF, African Vaccine Regulatory Forum; NRA, National Regulatory Authority; WHO, World Health Organization[33].

[g] Fast tracked
[h] New vaccines
[i] For priority global health products

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