Improving Access to Maternal Vaccines in Low-Resource Settings With Novel Packaging and Delivery Technologies: Summary of Project Results

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Introduction

Maternal immunization has the potential to protect both the mother and the infant during the vulnerable neonatal period. For infants, this protection is conferred not only indirectly by protecting the mother, but also directly through transplacental transfer of maternal immunoglobulin G antibodies.[1] Although immunoglobulin A antibodies cannot be transferred to the infant they can be useful through inducing mucosal immunity and providing secretory immunoglobulin A antibodies on the vaginal mucosa, which is the site of mother-to-child transmission. Generally, inactivated vaccines are considered safe during pregnancy.[2] Anaphylaxis during pregnancy is rare and there is no available evidence on the state of pregnancy increasing the risk of anaphylaxis.[3] Further research is also needed to explore whether the state of pregnancy increases the risk of respiratory side effects.

As maternal immunization gains momentum as a global health priority, vaccines that are in development and those that are currently available are being considered by global stakeholders and country ministries of health for inclusion in routine antenatal care (ANC).

Understanding the impact of presentation and packaging formats will be critical to preemptively optimizing vaccine products for the program and user requirements of ANC delivery scenarios in order to achieve global goals for maternal and newborn health. To date, a number of different packaging and delivery technologies have been developed that may improve safety, efficacy, cost- and program effectiveness, and ease of administration of some vaccines. These technologies can broadly be broken down into six categories including primary container technologies, intramuscular/subcutaneous injection technologies, intradermal injection technologies, respiratory formulation and delivery technologies, sublingual formulation and delivery technologies, and other alternative routes of delivery. These technologies are at varying stages of readiness and may pair with different vaccines in different formats, for different environments of use.

Under the grant "Improving access to adult vaccines in low-resource settings with novel packaging and delivery technologies," PATH explored the potential for high-priority maternal vaccines to be paired with different novel packaging and delivery technologies. We completed this work with three objectives and five activities:

Objectives	Activities
Objective 1. Determine the current state of the market for maternal immunizations and assess stakeholder requirements (six countries).	Activity 1. Define public health and programmatic priorities in six countries. Activity 2. Assess landscape of commercially available and pipeline vaccines for maternal immunization. Activity 3. Describe market requirements for selected vaccines.
Objective 2. Characterize maternal immunization delivery scenarios and identify constraints to increased coverage (two countries).	Activity 4. Describe programmatic constructs, constraints, and barriers for maternal and other adult vaccination in two countries.

Objectives	Activities
Objective 3. Map packaging and delivery technologies to address requirements and constraints identified under Objectives 1 and 2.	Activity 5. Map packaging and delivery technologies to address requirements and constraints.

We completed the work between January 2015 and September 2017. For each objective, we generated a final report to describe in detail the results of each activity. The reports and associated attachments are presented as Annexes 1 to 3. This summary provides an overview of key findings from the entirety of the project and references the detailed results presented in each report.

Objective 1. Determine the current state of the market for maternal immunizations and assess stakeholder requirements

Under this objective, we conducted primary and secondary research to collect data on countries' top priorities for maternal immunization and to characterize the market for maternal immunizations in select low- and middle-income countries. We outlined the landscape of vaccines with known and potential value in maternal immunization, and summarized global stakeholder and country-level program priorities for maternal immunization programs. We also generated preliminary demand estimates for high-priority maternal vaccines and summarized regulatory requirements for maternal vaccination. The outcomes of this work then informed the design of the country-specific needs assessments conducted under Objective 2 and the technology mapping exercise completed under Objective 3.

Key findings

Detailed results for each of the activities conducted under Objective 1 are presented in the report titled, *Phase I Summary Report: Maternal Immunization: Country Priorities and Market Requirements* (Annex 1). The key result from this phase was the exploration of priorities for maternal immunization through an online survey of global- and country-level stakeholders. The resulting list of high-priority vaccines then became a foundational element of the vaccine-technology mapping exercise conducted in Objective 3.

Country-level maternal immunization priorities

A survey of 14 countries, administered online, showed that barriers to vaccinating pregnant women include those related to clients' personal choices, such as lack of awareness, low ANC participation, concern regarding fetal safety, cost, and cultural bias. Survey responses came from individuals working within ministries of health, national immunization programs, and national and international nongovernmental organizations, including UNICEF and World Health Organization (WHO). One primary respondent was selected from each country based on expertise of respondents and completeness and consistency of data. Results also identified programmatic barriers including inadequate reach of the health system to marginal populations and lack of integration of maternal immunization into existing programs. Country-level stakeholders ranked increasing demand among pregnant women, setting maternal immunization policy, and training health care providers as top programmatic priorities.

In addition to the personal and programmatic barriers and the lack of consensus on which vaccines to prioritize for maternal immunization between global- and country-level stakeholders, regulatory requirements are another hurdle to consider once vaccines are ready for use. The regulatory capacity of National Regulatory Authorities in low- and middle-income countries is generally limited, and guidance on labeling vaccines for use in special high-risk populations such as pregnant women can be vague or nonexistent, thereby impeding product development, approval, and launch. Guidance from WHO and collaboration with countries via regional regulatory harmonization initiatives and other mechanisms will support these efforts.

High-priority vaccines

Global-level stakeholders identified five high-priority vaccines for addressing maternal and neonatal burden of disease: tetanus toxoid, inactivated influenza vaccine, Group B *Streptococcus*, respiratory syncytial virus, and pertussis vaccines (Table 1). However, among stakeholders at the country level, these priorities shifted to include hepatitis B vaccine as a high-priority vaccine among those that are already prequalified instead of inactivated influenza vaccine and pertussis, and to exclude Group B *Streptococcus* and respiratory syncytial virus vaccines among those that are still in development. Country-level stakeholders also identified malaria, hepatitis C, and dengue as high-priority diseases without currently prequalified vaccines. Tetanus toxoid was the only vaccine that was considered a high-priority vaccine by both global- and country-level stakeholders.

Table 1. Comparison of global-level and country-level stakeholders' high-priority vaccines.

Global experts	Country experts
1. TT*	**1. Hepatitis B***
2. IIV*	**2. Malaria**
3. GBS	**3. Hepatitis C**
4. RSV	**4. TT***
5. Tdap (pertussis)*	**5. Dengue**

Abbreviations: GBS, Group B *Streptococcus*; IIV, inactivated influenza vaccine; RSV, respiratory syncytial virus; Tdap, tetanus-diphtheria-acellular pertussis (low-dose diphtheria); TT, tetanus toxoid.

*Currently available and approved for use during pregnancy.

Objective 2. Characterize maternal immunization delivery scenarios and identify constraints to increased coverage

Under Objective 2, we conducted country-specific needs assessments in order to understand the context of use and intersection of provision of ANC services and maternal vaccination activities at the country level, using two countries (South Africa and El Salvador) as case studies. The objectives of the needs assessments were to:

1. Describe the programmatic scenarios of delivery of ANC.
2. Describe constraints and needs for optimizing access to maternal immunizations in ANC.
3. Describe provider perceptions regarding novel delivery technologies for administering maternal immunizations.

We used in-depth key stakeholder interviews with maternal immunization and ANC providers and experts, combined with contextual inquiry at health facilities to collect data on the delivery settings, constraints, and provider perceptions related to maternal immunization. Results of phase II are summarized in the report titled, *Phase II Summary Report: Maternal Immunization in South Africa and El Salvador: Case studies of constraints to uptake and introduction of maternal vaccines* (Annex 2). Detailed case reports on both South Africa and El Salvador are available in *Phase II Sub-attachment A: South Africa Maternal Immunization Needs Assessment: Summary of results* (Annex 2A) and *Phase II Sub-attachment B: El Salvador Maternal Immunization Needs Assessment: Summary of Results* (Annex 2B).

Key findings

We consolidated the constraints identified during the two country-based assessments in South Africa and El Salvador into a set of 10 needs relevant to packaging and delivery technologies (Table 2). These constraints can be classified into five major categories: (1) patient load, (2) limited cold chain, (3) limited sharps disposal, (4) variable training, and (5) access limitations. By identifying specific needs associated with these constraints, they could then be mapped to packaging and delivery technologies that can best address the needs in order to identify those packaging and delivery technologies with the greatest programmatic feasibility and potential for greatest impact.

Table 2. Constraints identified through needs assessments.

Constraints	Description	To address constraints, health care workers need a packaging/delivery technology that can:
Patient load	Excessive patient volumes. Long wait times can result in loss to follow up. Improvised timesaving measures, like prefilling syringes (which is against policy). Dose-tracking and dose-scheduling challenges.	Reduce preparation time (the time it takes to prepare the vaccine prior to administration). Reduce delivery time (the time it takes to administer the vaccine, once it is prepared for delivery). Enable task shifting to minimally trained health workers. Optimize dose per container: Enables EPI stakeholders to rightsize the doses per container according to the target environment of use.
Limited cold chain	Use of vaccine carriers to store daily supplies can result in accidental temperature excursions. Insufficient thermometers or other temperature indicators to ensure appropriate temperature conditions.	Increase thermostability to enhance cold chain flexibility and prevent vaccine damage during temperature excursions.

Constraints	Description	To address constraints, health care workers need a packaging/delivery technology that can:
	Transportation challenges can exacerbate cold chain limitations. Vaccine vial monitors are not used consistently on all vials and are not consistently checked.	
Limited sharps disposal	Usable sharps containers are not consistently available in antenatal care rooms to properly dispose of sharps waste. Community health workers who provide home-based care must give injections while juggling all their supplies, which can increase needlestick injury risk.	Reduce sharps waste. Minimize weight and bulk of supplies that community health workers need to transport to villages.
Variable training	High staff turnover and/or duty rotation results in varying levels of training and missed opportunities for refresher training.	Minimize training/literacy requirements. Enable task shifting to minimally trained health workers.
Access limitations	Community health workers have to carry heavy vaccine carriers and supplies with them to the community via public transportation to administer vaccines.	Optimize dose per container: Enables EPI stakeholders to rightsize the doses per container according to the target environment of use. Reduce glass waste. Minimize weight and bulk of supplies that community health workers need to transport to villages. Ensure robust packaging to prevent damaged/broken supplies.

Objective 3. Map packaging and delivery technologies to address requirements and constraints identified under Objectives 1 and 2

In this final phase of the project work, we drew on the results of Objectives 1 and 2 to develop a framework for pairing high-priority vaccines with novel packaging and delivery technologies. The purpose of this work was to identify optimized product presentations to address the constraints identified under Objective 2, as well as broader technical feasibility and program feasibility requirements. This mapping exercise followed a four-step process:

1. Identify high-priority vaccines and potential packaging/delivery technologies.
2. Eliminate nonviable vaccine-technology product pairs.
3. Prioritize pairs based on product attributes and identify pairs with the greatest potential net benefit to immunization delivery.

4. Map prioritized product pairs to the needs identified under Objective 2 and propose product pairs with the best potential to optimize introduction and uptake of maternal vaccines.

In step 1, we characterized currently used presentations of the high-priority vaccines that were first identified under Objective 1. Next, we paired together high-priority vaccines and key technologies. We consulted vaccine experts with expertise in innovative formulation, packaging and delivery technologies to determine the technical feasibility for each vaccine-technology pairing based upon the natural route of infection, vaccine type, use of adjuvants and preservatives, and context of use. For investigational vaccines, if there was no available evidence on compatible preservatives or anticipated vial size, they were assumed to be in single-dose vials with no preservative. We filtered out nonviable pairs and only the viable pairs that are potentially compatible with vaccine formulation and context of use were advanced to the next step. Following elimination of nonviable pairs, we scored all viable vaccine-technology pairs on a set of evaluation criteria based on vaccine product attributes, using the *Phase III Matrix: Vaccine Technologies Prioritization Tool* (Annex 3A). PATH led the development of this tool with input from experts such as members of IFPMA, including Pfizer representatives, as well as WHO and the IPAC Delivery Technologies Working Group. The tool's development included extensive prioritization and landscaping efforts vetted by the contributing partners. The tool is described further in the Objective 3 final presentation titled, *Phase III PPT: Improving access to maternal vaccines in low-resource settings with novel packaging and delivery technologies (Results of Objective 3: Optimal pairings of maternal vaccines with packaging/delivery technologies)* (Annex 3).

The prioritization tool generated a weighted score that indicated the programmatic and technical benefit of each vaccine-technology pair compared to the current presentation. We then mapped the needs identified under Objective 2 against those optimal pairs that were found to offer the potential for significant benefit over existing delivery formats (step 4). Secondary pairs found to potentially offer some benefit over existing formats are also listed in Annex 3. However, because their technical and programmatic feasibility require further consideration we did not map these pairs to the needs identified under Objective 2.

The final vaccine-technology pairings that are recommended for further evaluation are presented below with an overview of the technical development status and the potential programmatic benefits compared to the current presentation. The ANC scenario-specific needs that the product pair would address are also included.

Key findings

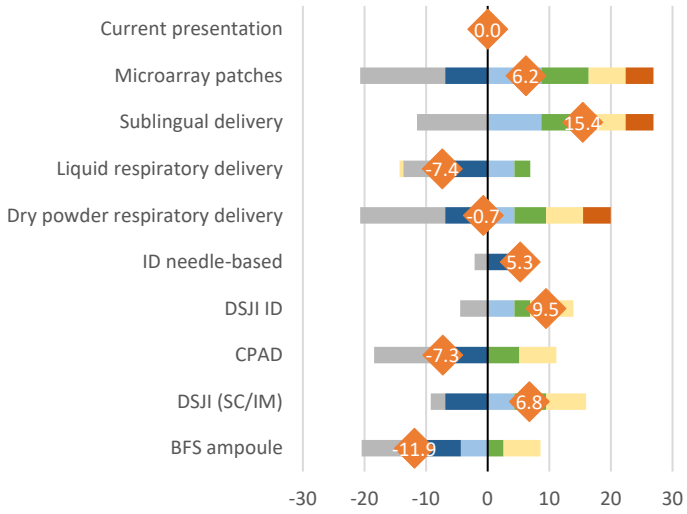
Figure 1 summarizes the output of the vaccine-technology prioritization activity and the needs mapping exercises that were conducted under this objective. Each of the charts below demonstrates how the optimal vaccine-technology pairs performed against six key criteria in the vaccine-technology prioritization exercise. A product pair with an average weighted score (orange marker) greater than 10 was considered to be an optimal pairing for the purposes of this evaluation. This optimal score represents a significant improvement over the current presentation (0, representing neutral value) and addresses at least 50 percent of the needs identified during this assesssment. The complete matrix that describes how each product pair maps to the needs identified in Objective 2 is presented in the Technology Prioritization Matrix document, which is appended to the Objective 3 final report.

Figure 1. Results of vaccine-technology pairing and needs mapping.

LEGEND

Technical/ manufacturing feasibility	COGS	Safety	Accessibility, usability, acceptability	Systems cost	Efficacy/ effectiveness

IIV Vaccine



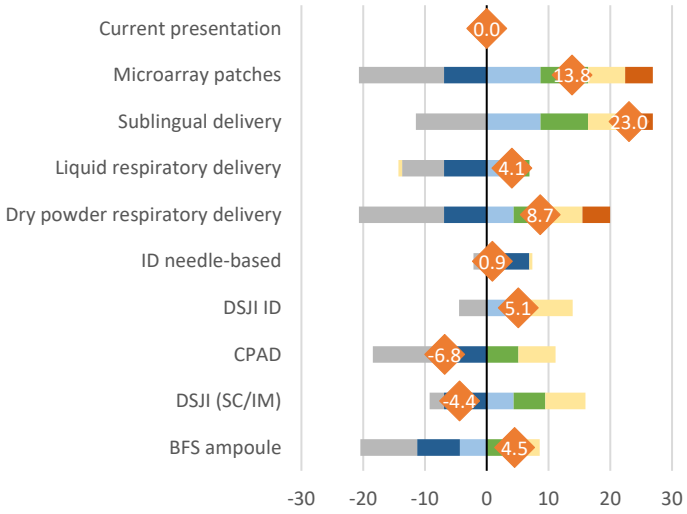
IIV + sublingual delivery

Sublingual delivery could be beneficial for IIV because it would deliver the vaccine directly to the mucosa where influenza enters the body via mucosal surfaces in the respiratory tract as well as provide mucosal immunity. A sublingual IIV vaccine was shown to be immunogenic in preclinical animal studies.[4] Moreover, this technology is needle-free, may improve thermostability, and can potentially be used by health workers of varying skill levels, which could enable task-shifting in some settings. Sublingual delivery of this vaccine could improve upon the current delivery format for 9 out of 10 of the needs identified in Objective 2, indicating that it could be optimally suited for use in ANC delivery scenarios.

LEGEND

Technical/ manufacturing feasibility	COGS	Safety	Accessibility, usability, acceptability	Systems cost	Efficacy/ effectiveness

GBS Vaccine



GBS vaccine + sublingual delivery

Sublingual delivery could be beneficial for this type of pathogen as GBS enters the body via the mucosa. Delivering the vaccine directly to the mucosa could theoretically provide mucosal immunity, including induction of sIgA antibody on the vaginal mucosa, which is the site of mother-to-child transmission.[5] A sublingual GBS vaccine was shown to be immunogenic in preclinical animal studies.[6] Moreover, this technology is needle-free, can improve thermostability, and can be easy to use by health workers of varying skill levels, which could enable task-shifting in some settings. Sublingual delivery of this vaccine could improve upon the current delivery format for 8 out of 10 of the needs identified in Objective 2.

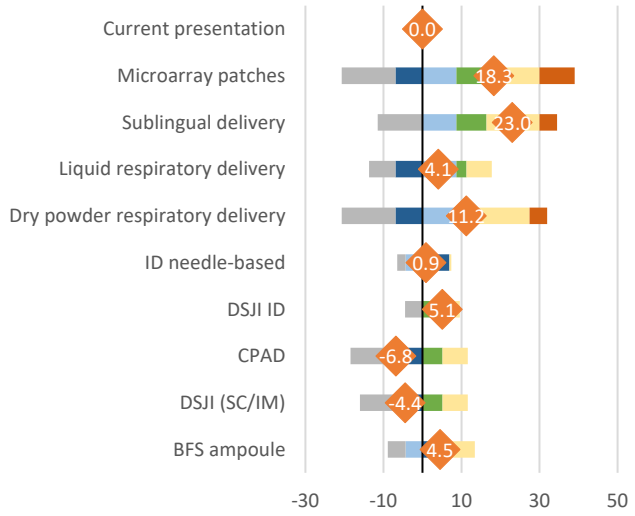
GBS vaccine + MAP)

Although a GBS vaccine MAP is possible based on the pathogen and natural route of infection, research on this vaccine-technology combination has not been published. A GBS vaccine MAP could improve usability, acceptability, and accessibility while improving thermostability and eliminating needles. This product could improve upon the current delivery format for 8 out of 10 of the needs identified in Objective 2.

LEGEND

Technical/ manufacturing feasibility	COGS	Safety	Accessibility, usability, acceptability	Systems cost	Efficacy/ effectiveness

RSV Vaccine



RSV vaccine + dry-powder respiratory delivery

(DPRD could be beneficial for RSV vaccine because it would deliver the vaccine directly to mucosal surfaces in the respiratory tract where RSV enters the body and provide mucosal immunity. Although DPRD has not been tested for RSV vaccine, a liquid respiratory vaccine has been shown to be immunogenic in preclinical animal studies and is currently being tested in a phase I clinical trial in adults.[7] A lyophilized RSV vaccine has also been tested in mice, which demonstrates the potential to reformulate a liquid RSV vaccine into a dry presentation.[8] Moreover, these delivery technologies are needle-free, can improve thermostability, and the technology is potentially suitable for use by most levels of health worker, which could enable task-shifting in some settings. DPRD could improve upon the current delivery format for 5 out of 10 of the needs identified in Objective 2.

RSV vaccine + sublingual delivery

Sublingual delivery could be beneficial for this type of pathogen as RSV enters the body via the mucosa and this type of device delivers vaccine directly to the mucosa, thus providing mucosal immunity. A sublingual RSV vaccine was shown to be immunogenic in preclinical animal studies.[9] This technology is needle-free, can improve thermostability, and could be easy to use by health workers of varying skill levels, which could enable task-shifting in some settings. Sublingual delivery of this vaccine could improve upon the current delivery format for 8 out of 10 of the needs identified in Objective 2.

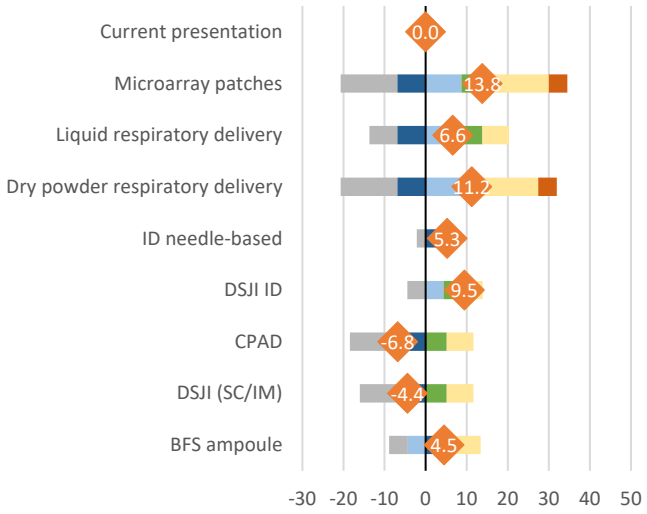
RSV vaccine + MAPs

Although an RSV vaccine MAP is possible based on the pathogen and natural route of infection, no candidates in development could currently be identified. An RSV vaccine MAP could improve usability, acceptability, and accessibility while improving thermostability and eliminating needles. A MAP presentation of this vaccine could improve upon the current delivery format for 8 out of 10 of the needs identified in Objective 2.

LEGEND

Technical/ manufacturing feasibility	COGS	Safety	Accessibility, usability, acceptability	Systems cost	Efficacy/ effectiveness

Hepatitis C Vaccine



Hepatitis C vaccine + dry-powder respiratory delivery

DPRD could be beneficial for this type of pathogen because it would deliver the vaccine directly to the mucosal surfaces, which is the site of mother-to-child transmission, and provide mucosal immunity. A DPRD for hepatitis C vaccine is possible based on the pathogen and natural route of infection. However, no candidates in development could currently be identified. DPRD is needle-free, can improve thermostability, and the technology has the potential to be easy to use by most levels of health worker, which could enable task-shifting in some settings. This format could improve upon the current delivery format for 5 out of 10 of the needs identified in Objective 2.

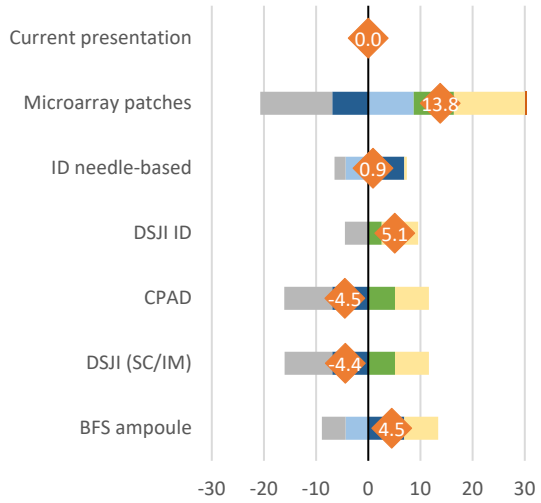
Hepatitis C vaccine + MAPs

A hepatitis C vaccine MAP was shown to be immunogenic in a preclinical study in mice immunized with a hepatitis C DNA vaccine-coated MAP.[10] MAPs are needle-free, can improve thermostability, and the technology is easy to use by most levels of health worker, enabling task-shifting in some settings. A MAP presentation of this vaccine could improve upon the current delivery format for 7 out of 10 of the needs identified in Objective 2, indicating that it is optimally suited for use in ANC delivery scenarios.

LEGEND

Technical/ manufacturing feasibility	COGS	Safety	Accessibility, usability, acceptability	Systems cost	Efficacy/ effectiveness

Dengue Vaccine



Dengue vaccine + MAPs

Although a dengue vaccine MAP is possible based on the pathogen and natural route of infection, no candidates were identified. A dengue vaccine MAP could improve usability, acceptability, and accessibility while improving thermostability and eliminating needles. A MAP presentation of this vaccine could improve upon the current delivery format for 8 out of 10 of the needs identified in Objective 2.

Abbreviations: ANC, antenatal care; BFS, blow-fill-seal; COGS, cost of goods sold; CPAD, compact, prefilled, autodisable device; DPRD, dry-powder respiratory delivery; DSJI, disposable-syringe jet injector; GBS, Group B *Streptococcus*; ID, intradermal; IIV, inactivated influenza vaccine; IM, intramuscular; MAP, microarray patch; RSV, respiratory syncytial virus; SC, subcutaneous; sIgA, secretory Immunoglobulin A.

Conclusions

The mapping exercise conducted under Objective 3, which drew on the results from Objectives 1 and 2, demonstrated that dry-powder respiratory delivery, sublingual delivery, and microarray patches offer promising means to optimize maternal vaccine products for improving uptake of existing vaccines and streamlining introduction of new vaccines. In addition, intradermal needle-based technologies; intradermal disposable-syringe jet injectors; blow-fill-seal containers; compact, prefilled, autodisable devices; liquid respiratory delivery; and subcutaneous/intramuscular disposable-syringe jet injectors may also offer some advantage over current packaging and delivery methods. For each of these potential pairings, gaps in data or potential challenges with feasibility and programmatic suitability should be explored further before pursuing new product development. The scores for these pairings are particularly influenced by the lack of data from studies conducted with pregnant women. In most cases, these vaccine-technology pairings have only been evaluated in preclinical animal studies and clinical trials have only been conducted with nonpregnant adults.

In many cases, the most promising pairings that we presented as the culmination of this project work are further upstream in the product development pipeline and would require greater investments in technical development, manufacturing facilities, and the clinical/regulatory pathway than current presentations and delivery formats. These novel packaging and delivery technologies would also require an extensive body of safety data before they could be licensed in a vulnerable population like pregnant women. This is the nature of building novel products; further assessment would be required to fully explore the potential of such an investment. In some cases, vaccine-technology pairings identified to have a more modest potential benefit for immunization systems could potentially be more feasible to develop and implement. Technologies paired with currently approved vaccines like influenza and tetanus toxoid may be more feasible to license since these vaccines have a long history of use in pregnant women and robust safety records. A comprehensive total-systems effectiveness analysis would be required for any vaccine-technology pairing to fully characterize the potential total cost and health impact that a particular technology pairing could have on maternal and newborn health outcomes.

To better understand the value proposition of these optimal pairings, further in-country analysis of acceptability and operational fit will be required. In particular, the acceptability of vaccines designed to protect the infant without providing direct benefits to the mother should be explored. Moreover, before new vaccine-technology pairings can be introduced, a robust evidence base will be needed in order to fully characterize how the state of pregnancy changes the risk of side effects and adverse events related to specific vaccines. Therefore the amount of new data needed to achieve licensure for each vaccine-technology pairing is likely to depend on the existing safety data for the independent vaccine and technology components, meaning that more novel pairings may require significantly more investment than pairings of vaccines with technologies that are each already licensed independently.

References

1. Englund J, Glezen WP, Piedra PA. Maternal immunization against viral disease. *Vaccine.* 1998;16(14):1456–1463.

2. Omer SB. Maternal Immunization. *New England Journal of Medicine*. 2017;376(13):1256–1267. doi: 10.1056/NEJMra1509044.

3. Simons FE, Schatz M.. Anaphylaxis during pregnancy. *Journal of Allergy and Clinical Immunology*. 2012;130(3): 597–606. doi: 10.1016/j.jaci.2012.06.035

4. Mann JF, Tregoning JS, Aldon Y, Shattock RJ, McKay PF. CD71 targeting boosts immunogenicity of sublingually delivered influenza haemagglutinin antigen and protects against viral challenge in mice. *Journal of Controlled Release*. 2016;232:75–82.

5. Patras KA, Rösler B, Thoman ML, Doran KS. Characterization of host immunity during persistent vaginal colonization by Group B *Streptococcus*. *Mucosal immunology*. 2015;8(6):1339–1348.

6. Shen X, Lagergård T, Yang Y, Lindblad M, Fredriksson M, Holmgren J. Systemic and mucosal immune responses in mice after mucosal immunization with group B streptococcus type III capsular polysaccharide-cholera toxin B subunit conjugate vaccine. *Infection and Immunity*. 2000;68(10):5749–5755.

7. Chiu C. Phase I Study for SynGEM, an Intranasal Respiratory Syncytial Virus (RSV) Prefusion F Subunit Candidate Vaccine (SynGEM). Available at: https://clinicaltrials.gov/ct2/show/NCT02958540.

8. Levine S, Dillman TR, Montgomery PC. The envelope proteins from purified respiratory syncytial virus protect mice from intranasal virus challenge. *Proceedings of the Society for Experimental Biology and Medicin*e. 1989;190(4):349–356.

9. Lee JY, Chang J. Universal vaccine against respiratory syncytial virus A and B subtypes. *PLoS One*. 2017 Apr 6;12(4):e0175384. doi: 10.1371/journal.pone.0175384.

10. Gill HS, Sõderholm J, Prausnitz MR, Sällberg M. Cutaneous vaccination using microneedles coated with hepatitis C DNA vaccine. *Gene Therapy*. 2010;17(6):811–814.

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]

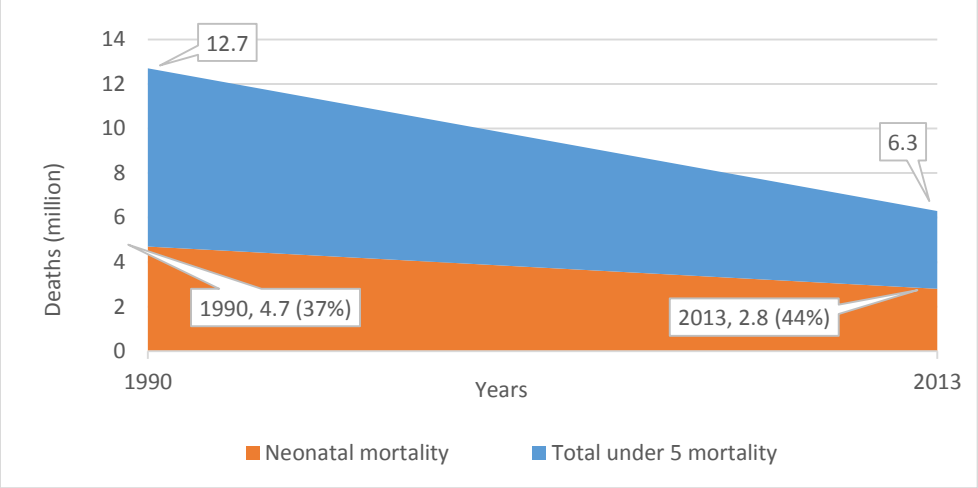


Figure 1. Neonatal mortality as a proportion of total under-5 mortality, 1990 and 2013.

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.

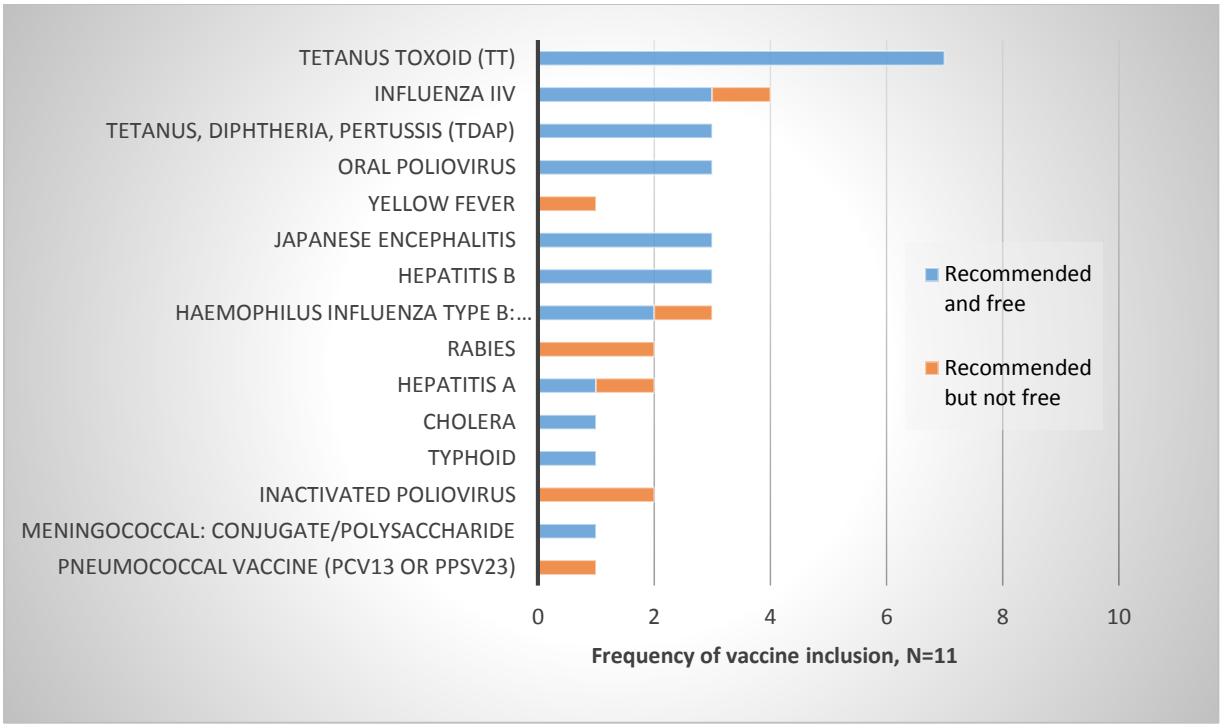


Figure 2. Vaccines included in immunization strategies in countries participating in the survey.
Note: IIV, inactivated influenza vaccine.

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.

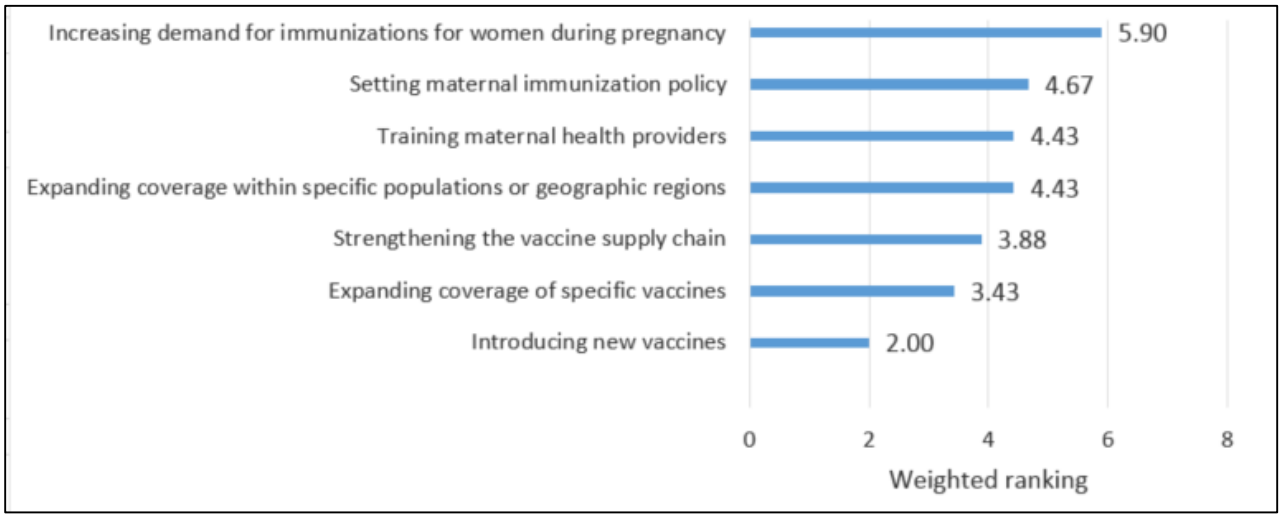


Figure 3. Weighted ranking of high-priority programmatic issues for maternal immunization.

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.

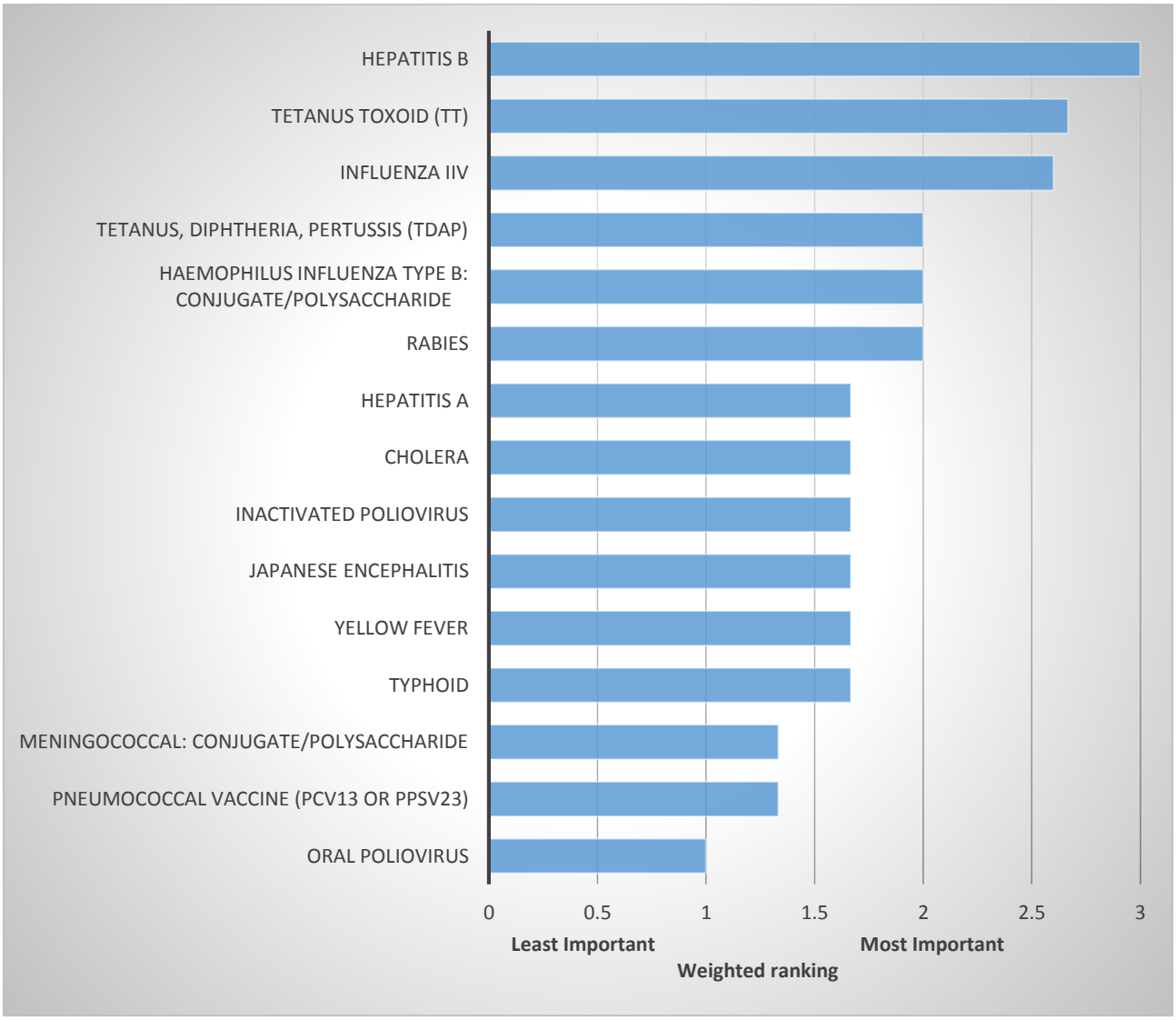


Figure 4. Countries' maternal immunization priorities for vaccines currently prequalified by the World Health Organization.
Note: IIV, inactivated influenza vaccine.

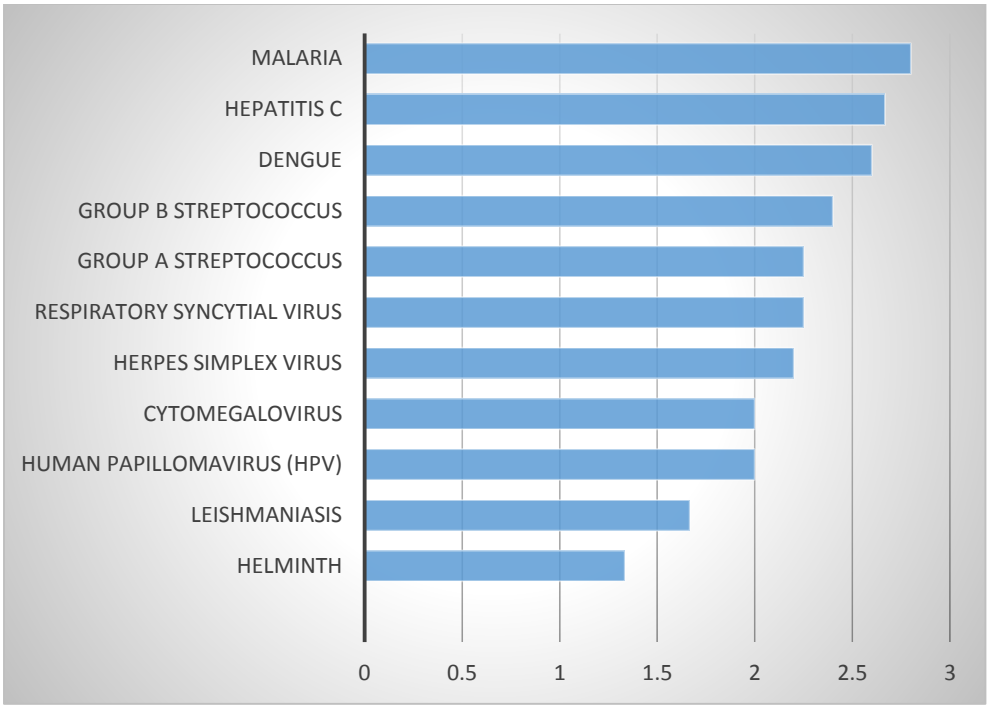


Figure 5. Countries' maternal immunization priorities for vaccines under development or not currently prequalified by the World Health Organization.[c]

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.

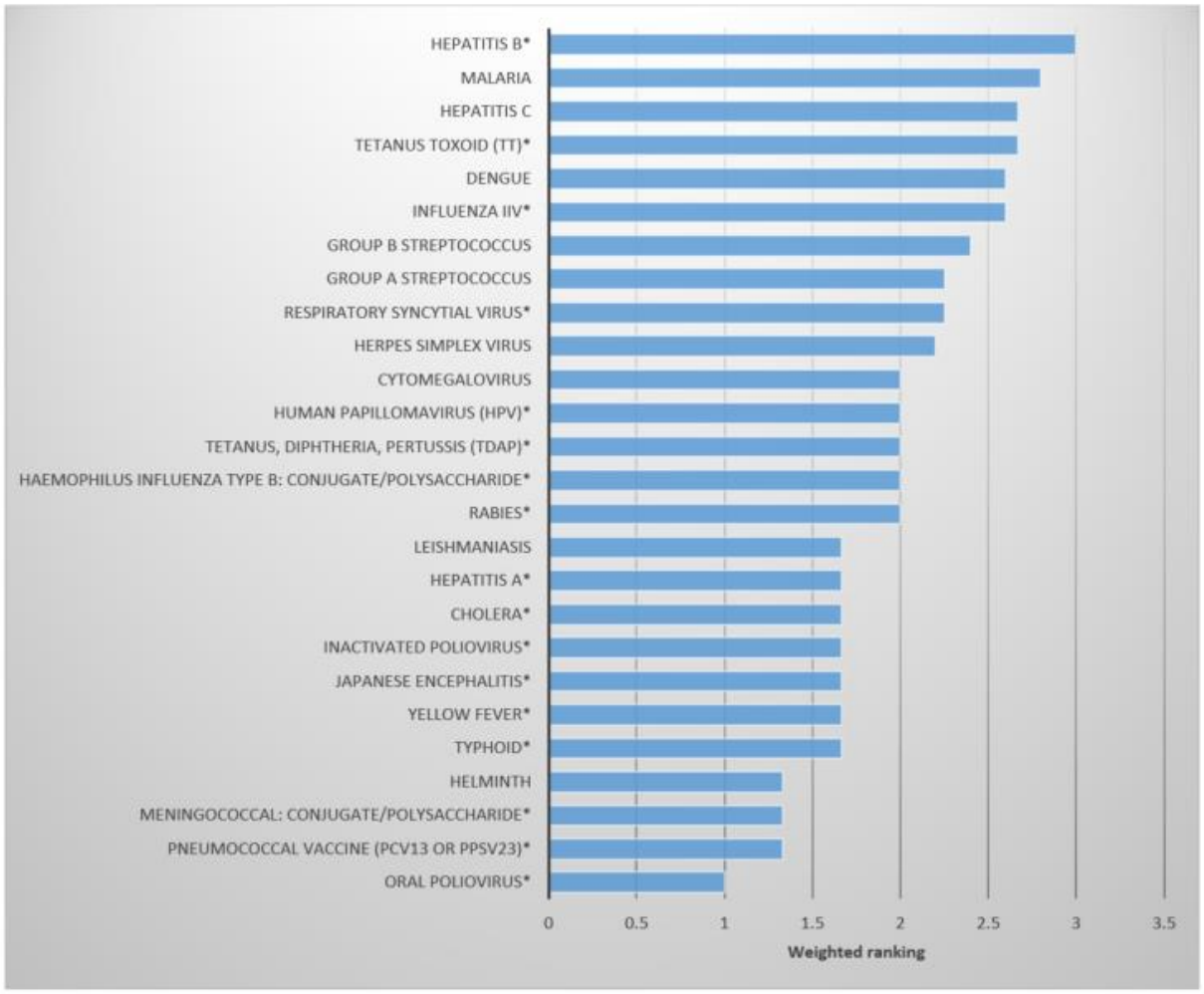


Figure 6. Combined maternal immunization priority vaccines listed by national stakeholders—currently prequalified and possible future vaccines (N = 14).
**Currently available vaccine.*

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.

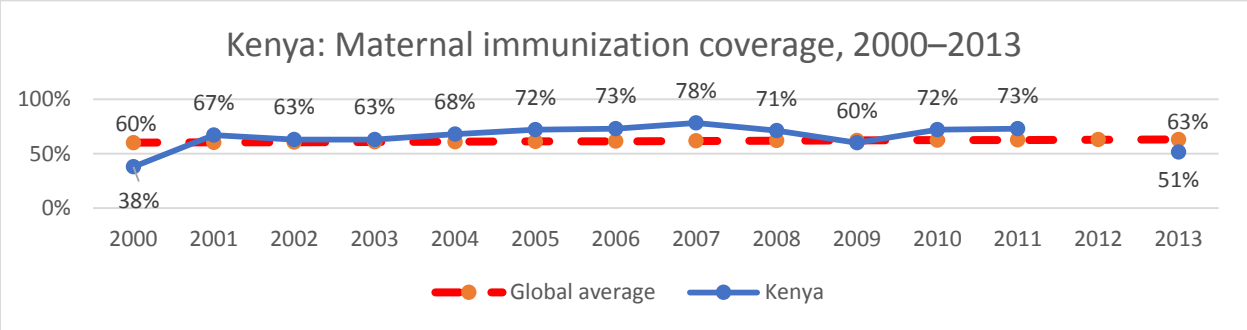
Programmatic priorities include increasing demand for immunizations among women during pregnancy, training maternal health providers to deliver vaccines, and integrating maternal immunizations with other health programs.

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

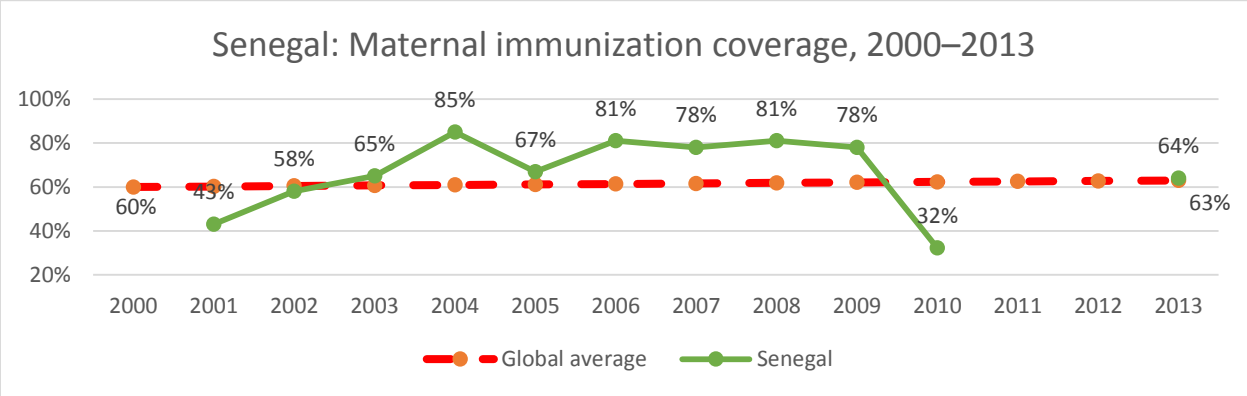
Senegal has achieved elimination of tetanus and includes maintaining eliminated status within its objectives for the EPI.[47] The Senegal EPI Comprehensive Multiyear Plan list includes reaching 90% coverage for TT2+. No other maternal vaccines are included in the multiyear plan.[48]

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

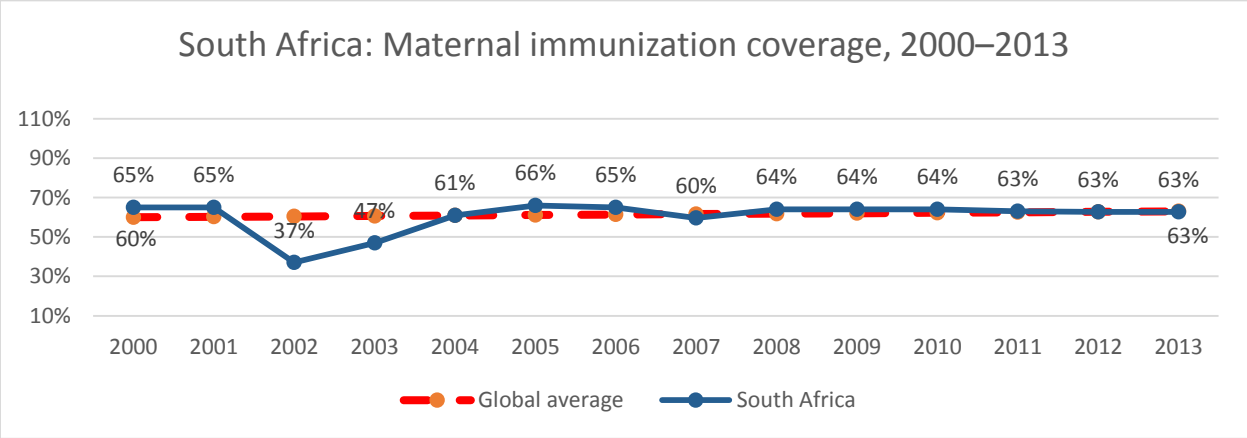
The maternal immunization program of South Africa has achieved an estimated TT2+ vaccine coverage of between 40 percent and 60 percent. However, maternal immunization is not effectively monitored, so there are insufficient data regarding rates of coverage and barriers to uptake. Maternal vaccine supply 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.

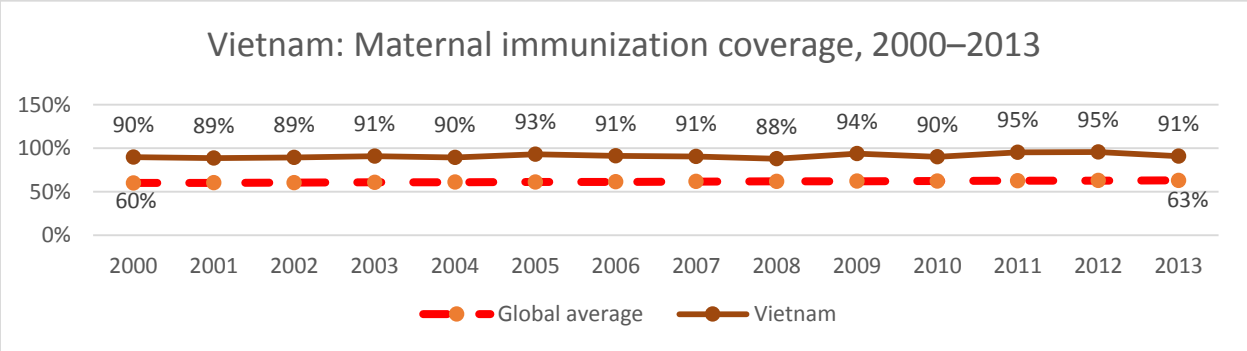
Image: WHO

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

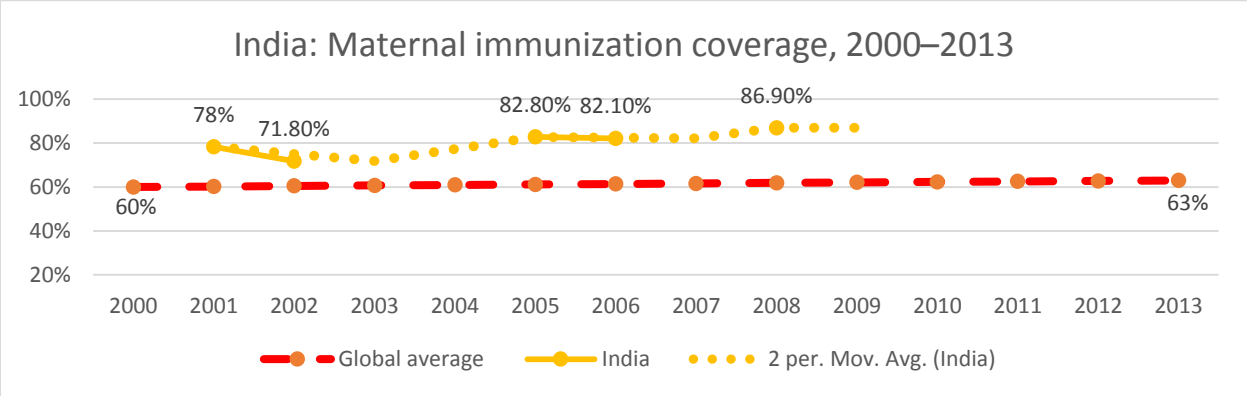
The Indian maternal immunization program has been in place for more than five years and has achieved an estimated TT vaccine coverage of between 60 percent and 80 percent. Maternal vaccine procurement and distribution are integrated into maternal and child health strategy in India. Health systems factors 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

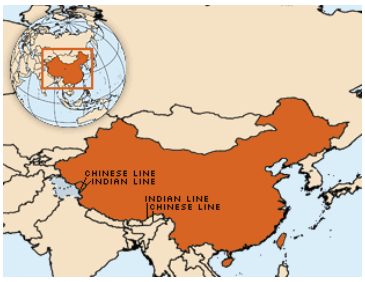


Image: WHO

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

[1] Newborn death and illness page. World Health Organization, The Partnership for Maternal Newborn & Child Health (PMNCH) website. Available at: http://www.who.int/pmnch/media/press_materials/fs/fs_newborndealth_illness/en/. Accessed December 2, 2015.

[2] Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. *New England Journal of Medicine.* 2008;359(15):1555–1564.

[3] Maclennan R, Schofield FD, Pittman M, Hardegree MC, Barile MF. Immunization against neonatal tetanus in New Guinea. Antitoxin response of pregnant women to adjuvant and plain toxoids. *Bulletin of the World Health Organization.* 1965;32:683–697.

[4] Newell KW, Lehmann AD, LeBlanc DR, Osorio NG. The use of toxoid for the prevention of tetanus neonatorum: Final report of a double-blind controlled field trial. *Bulletin of the World Health Organization.* 1966;35(6):863–871.

[5] Schofield FD, Tucker VM, Westbrook GR. Neonatal tetanus in New Guinea. Effect of active immunization in pregnancy. *British Medical Journal*. 1961;2(5255):785–789.

[6] Waaijenborg S, Hahné SJ, Mollema L, et al. Waning of maternal antibodies against measles, mumps, rubella, and varicella in communities with contrasting vaccination coverage. *Journal of Infectious Diseases*. 2013;208(1):10–16.

[7] Englund J, Glezen WP, Piedra PA. Maternal immunization against viral disease. *Vaccine.* 1998;16(14):1456–1463.

[8] World Health Organization (WHO), United Nations Children's Fund (UNICEF), World Bank. *State of the World's Vaccines and Immunization*. Geneva: WHO; 2009. Available at: http://apps.who.int/iris/bitstream/10665/44169/1/9789241563864_eng.pdf. Accessed December 2. 2015.

[9] Expanding immunization coverage page. United Nations Children's Fund website. Available at: http://www.unicef.org/immunization/index_coverage.html. Accessed September 18, 2014.

[10] Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. *The Lancet.* 2015:385(9966):430–440.

[11]UNICEF. *Committing to Child Survival: A Promise Renewed. Progress Report 2014.* New York: UNICEF; 2014. Available at: http://www.apromiserenewed.org/APR_2014_web_15Sept14.pdf. Accessed December 2, 2015.

[12] Edmond K, Zaidi A. New approaches to preventing, diagnosing, and treating neonatal sepsis. *PLoS Medicine*. 2010;7(3):283.

[13] Riley C, Wheeler DS. Prevention of sepsis in children: a new paradigm for public policy. *Critical Care Research and Practice*. 2012:437139.

[14] Global Burden of Disease Study 2013. *Global Burden of Disease Study 2013 (GBD 2013) Risk Factor Results 1990-2013.* Seattle, United States: Institute for Health Metrics and Evaluation (IHME); 2015.

[15] Global Health Observatory Data Repository page. WHO website. Available at: http://apps.who.int/gho/data/node.main.ChildMort100?lang=en. Accessed August 30, 2015.

[16] Yudin MH. Risk management of seasonal influenza during pregnancy: current perspectives. *International Journal of Women's Health*, 2104;6:681.

[17] Bill & Melinda Gates Foundation (BMGF). *2015 Maternal Immunization Stakeholder Convening Path to Impact.* Berlin, Germany: BMGF; 2015. Available at: http://www.who.int/immunization/sage/meetings/2015/april/2_2015_Sa03_20_FullReport_BMGF_MI_Convening.pdf.

[18] Pathirana J, Nkambule J, Black S. Determinants of maternal immunization in developing countries. *Vaccine*. 2015;33(26):2971–2977.

[19] Chu, HY, Englund JA. Maternal immunization. *Clinical Infectious Diseases*. 2014;59(4):560–568.

[20] US Centers for Disease Control and Prevention (CDC). General recommendations on immunization. *Morbidity and Mortality Weekly Report.* 2011;60(2):26. Available at: http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf. Accessed January 2, 2015.

[21] Skoff TH, Kenyon C, Cocoros N, Liko J, Miller L, Kudish K, Baumbach J, Zansky S, Faulkner A, Martin SW. Sources of Infant Pertussis Infection in the United States. *Pediatrics*. 2015;136(4):635–41.

[22] US Centers for Disease Control and Prevention (CDC). Guidelines for vaccinating pregnant women page. CDC website. Available at: http://www.cdc.gov/vaccines/pubs/preg-guide.htm. Accessed December 17, 2015.

[23] Maternal immunization research and implementation portfolio. Immunization, Vaccines and Biologicals page. WHO website. Available at: http://www.who.int/immunization/research/maternal_immunization/en/. Accessed January 2, 2015.

[24] Englund JA. Maternal immunization - Promises and concerns. *Vaccine*. 2015:33(47):6372-6373.

[25] World Health Organization. *Country Cooperation Strategy Kenya, Medium - Term Support Strategy 2014 – 2019.* Nairobi: WHO; 2014. Available at: http://www.afro.who.int/index.php?option=com_docman&task=doc_download&gid=9704&Itemid=2593. Accessed December 9, 2015.

[26] Khan R, Vandelaer J, Yakubu A, Raza AA, Zulu F. Maternal and neonatal tetanus elimination: from protecting women and newborns to protecting all. *International Journal of Women's Health*, 2105:7;171.

[27] Procurement mechanisms and systems. Immunization, Vaccines and Biologicals page. WHO website. Available at: http://www.who.int/immunization/programmes_systems/procurement/mechanisms_systems/pooled_procurement/en/index2.html. Accessed December 2, 2015.

[28] Priority setting for WHO vaccine prequalification. Immunization standards page. WHO website. Available at: http://www.who.int/immunization_standards/vaccine_quality/pq_priorities/en/. Accessed December 2, 2015.

[29] World Health Organization. *Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification*. Geneva: WHO; 2015. Available at: http://apps.who.int/iris/bitstream/10665/148168/1/WHO_IVB_14.10_eng.pdf. Accessed December 9, 2015.

[30] World Health Organization. WHO support for medicines regulatory harmonization in Africa: focus on East African Community. *WHO Drug Information.* 2014;28(1):11. Available at: http://www.who.int/medicines/publications/druginformation/DI_28-1_Africa.pdf. Accessed December 2, 2015.

[31] Global Health Technologies Coalition (GHTC). *The African Vaccine Regulatory Forum: An Introductory Guide for Product Developers.* Washington, DC: GHTC; (year unknown). Available at: http://www.ghtcoalition.org/files/AVAREFguide-final-formattedforrelease.pdf. Accessed December 8, 2015.

[32] World Health Organization. *9th Annual Meeting of the African Vaccine Regulatory Forum (AVAREF)*. Pretoria, South Africa: WHO; 2014. Available at: http://www.who.int/immunization_standards/vaccine_regulation/avaref_meeting_recommendations_14nov2014.pdf?ua=1. Accessed December 8, 2015.

[33] World Health Organization (WHO). *Guideline on Submission of Documentation for Prequalification of Multisource (Generic) Finished Pharmaceutical Products (FPPs) Approved by Stringent Regulatory Authorities (SRAs)*. QP09001/Ver.1. Geneva: WHO; 2011. Available at: http://apps.who.int/prequal/info_applicants/Guidelines/PQProcGenericSRA_July2011.pdf.

[34] Global Health Technologies Coalition. *GHTC Briefing Paper, Volume 4: Addressing Regulatory Challenges Throughout the Product Development Process: Perspectives From Nonprofits on Accelerating Product Development and Improving Access for Low- and Middle-Income Countries*. Washington, DC: GHTC; 2014. Available at: http://ghtcoalition.org/files/ER_GHTC_NPPD_briefing-paperVol_4_Final.pdf. Accessed December 8, 2015.

[35] World Health Organization. *Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification.* Geneva: WHO; 2014. Available at: http://apps.who.int/iris/bitstream/10665/148168/1/WHO_IVB_14.10_eng.pdf?ua=1. Accessed December 8, 2015.

[36] Vaccine Presentation and Packaging Advisory Group (VPPAG) page. WHO website. Available at: http://www.who.int/immunization/policy/committees/vppag/en/. Accessed December 17, 2015.

[37] US Food and Drug Administration (FDA). *Guidance for Industry and FDA Staff: Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA.* Silver Springs, Maryland: US FDA; 2013. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM336230.pdf. Accessed December 8, 2015.

[38] US Food and Drug Administration. *FDA Updated Communication on Use of Jet Injectors with Inactivated Influenza Vaccines*. Silver Springs, Maryland: US FDA; 2014. Available at: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/QuestionsaboutVaccines/ucm276773.htm. Accessed December 8, 2015.

[39] Roberts JN, Gruber MF. Regulatory considerations in the clinical development of vaccines indicated for use during pregnancy. *Vaccine* (2015), http://dx.doi.org/10.1016/j.vaccine.2014.12.068

[40] US Food and Drug Administration. *Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications*. Rockland, Maryland: Silver Springs, Maryland: US FDA; 2006. Available at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074827.htm. Accessed December 8, 2015.

[41] Mastroianni, A, Faden R, and Federman D, eds. *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*. Vol. 2. Washington, DC: National Academies Press; 1994.

[42] Gruber MF. Maternal immunization: US FDA regulatory considerations. *Vaccine.* 2003;21(24):3487–3491.

[43] Roberts J. Regulatory considerations for RSV vaccine development. Presented at: WHO Consultation on RSV Vaccine Development, March 23–24, 2015; Geneva, Switzerland. Available at: http://www.who.int/immunization/research/meetings_workshops/FDA_regulatory_perspective_RSV_vaccines_Roberts.pdf. Accessed December 8, 2015.

[44] WHO Technology, Norms and Standards team and Initiative for Vaccine Research team. WHO consultation on influenza vaccines for pregnant and lactating women: Clinical data requirements for product labelling. Presented at: Consultation WHO Headquarters, July 15–16, 2014; Geneva, Switzerland. Available at: http://www.who.int/biologicals/vaccines/INFLUENZA_VACCINES_Executive_Summary_FINAL_29_Sept_R.pdf. Accessed December 8, 2015.

[45] Package insert for TETATOX TT VACCINE tetanus vaccine (adsorbed). InterVax Toronto, Canada. Available at: http://www.who.int/immunization_standards/vaccine_quality/76_tet.pdf?ua=1. Accessed December 6, 2015.

[46] Saving Lives at Birth: A Grand Challenge for Development announces award nominees for innovative solutions to prevent infant/maternal deaths [press release]. Washington, DC: United States Agency for International Development (USAID); July 31, 2013. Available at: https://www.usaid.gov/news-information/press-releases/saving-lives-birth-grand-challenge-development-announces-award. Accessed December 8, 2015.

[47] Plan strategique national de communication pour la vaccination de routine 2014–2016. Le Service National de l'Éducation et de l'Information pour la Santé, Senegal. [National strategic communication plan for routine vaccination, 2014–2016. Senegal National Health Information & Education Service]. Available at: http://www.nationalplanningcycles.org/sites/default/files/planning_cycle_repository/senegal/pnscpev_de_routine_version_du_15_juillet2014.pdf. Accessed December 6, 2015.

[48] Republic of Senegal Ministry of Public Health and Prevention. *EPI Comprehensive Multiyear Plan; 2012–2016*. Dakar: Republic of Senegal; 2011. Available at: http://www.gavi.org/Country/Senegal/Documents/CMYPs/Comprehensive-multi-year-plan-for-2012-2016/.

[49] (Author not available.) South African vaccine maker boosts its continental reach. *Vaccine News Reports.* January 26, 2010.

[50] National regulatory authority of Viet Nam Meets international standards for vaccine regulation [press release]. Hanoi, Vietnam: WHO Representative Office; June 22, 2015. Available at: http://www.wpro.who.int/vietnam/mediacentre/releases/2015/nra_vietnam_certification/en/. Accessed December 8, 2015.

[51] International AIDS Vaccine Initiative (IAVI). *IAVI Policy Brief #16: Procurement and Pricing of New Vaccines for Developing Countries*. New York: IAVI; 2008. Available at: http://www.rho.org/files/IAVI_vaccine_procurement_pricing.pdf. Accessed December 8, 2015.

[52] World Health Organization. *Strengthening India's Vaccine Regulatory Authority*. Geneva: WHO; 2013. Available at: http://www.who.int/about/who_reform/change_at_who/india_vaccine_regulation/en/#.Vd9enLTzSFs. Accessed December 8, 2015.

[53] Shirodkar SN. CDSCO to go for massive recruitment drive, to appoint 5500 staff at Centre & states. *PharmaBiz.com.* July 14, 2014. Available at: http://pharmabiz.com/ArticleDetails.aspx?aid=82906&sid=1. Accessed December 8, 2015.

[54] Antenatal care coverage - at least one visit (%) - China page. Quand website. Available at: https://www.quandl.com/data/WHO/6400_157-Antenatal-care-coverage-at-least-one-visit-China. Accessed December 8, 2015.

[55] Harris A, Zhou Y, Liao H, Barclay L, Zeng W, Gao Y. Challenges to maternal health care utilization among ethnic minority women in a resource-poor region of Sichuan Province, China. *Health Policy and Planning.* 2010;25(4):311–318.

[56] Barry F. Does second prequalified vaccine mark China as "true global player?" *In-Pharma Technologist.com*. June 23, 2015. Available at: http://www.in-pharmatechnologist.com/Regulatory-Safety/Does-second-prequalified-vaccine-mark-China-as-true-global-player. Accessed December 8, 2015.

Maternal Immunization in South Africa and El Salvador: Case Studies of Constraints to Uptake and Introduction of Maternal Vaccines

SEPTEMBER 26, 2017

Submitted to Pfizer Independent Grants for Learning & Change

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For more information on PATH's work in vaccine and pharmaceutical technologies, visit: http://sites.path.org/vpt.

Contents

Abbreviations

ANC antenatal care

EPI Expanded Programme on Immunization

IIV inactivated influenza vaccine

Tdap tetanus, diphtheria, pertussis

TT tetanus toxoid

VVM vaccine vial monitor

Introduction

New maternal vaccines are progressing through product development and becoming ready for wide-scale introduction. Existing maternal vaccines are also being scaled up with broader global introduction efforts. It will be important in this context to have a detailed understanding of the relationship between the operational requirements for these new and underused vaccines and which product presentations will be most appropriate for the target settings for use. As part of a larger project that is exploring opportunities to improve uptake and introduction of maternal vaccines, PATH has undertaken a needs assessment in two countries, in settings where maternal vaccines are given. The goal of this activity was to determine possible barriers to optimal maternal vaccine coverage that can be addressed by novel and innovative packaging and delivery technologies for these vaccines. In 2016, we completed data collection in South Africa, which was identified during phase 1 of this project as a country with a robust maternal vaccination strategy and a range of types of delivery environments, making the country an optimal location for a needs assessment of this type.[1] In 2017, we conducted a similar assessment in El Salvador, which was selected because of the operational challenges it faces, its community-based approach to maternal immunization, and because it offers a unique perspective into the challenges faced in Latin American countries struggling with the Zika epidemic.

The results of these two needs assessments are summarized below, followed by a discussion of the needs identified and how they may inform selection of novel packaging and delivery options for new and underutilized maternal vaccines. For each country's individual results, please refer to the corresponding report, attached as appendices A and B.

Objectives

The goal of conducting the country-specific needs assessments was to use two countries' maternal immunization settings as case studies to understand the context of use and intersection of provision of antenatal care (ANC) services and maternal vaccination activities. The objectives of the needs assessments were:

1. Describe the programmatic constructs and scenarios of delivery of ANC.
2. Describe constraints and needs for optimizing access to maternal immunizations in ANC.
3. Describe provider perceptions regarding novel delivery technologies for administering maternal immunizations.

Methods

We conducted this qualitative needs assessment using in-depth key stakeholder interviews with maternal immunization and ANC experts, contextual inquiry at health facilities where we observed service delivery, and targeted interviews with health care workers who provide maternal vaccinations. To respect patient privacy, we did not conduct patient interviews. We also conducted secondary analysis of country-specific documents and policies. We aimed to interview maternal immunization and ANC experts at the regional, national, and local levels, including key stakeholders at the national program level and health workers in ANC and immunization settings. We used purposive sampling to select individuals who were

especially knowledgeable about maternal immunization to achieve depth of understanding of the topic of interest.

We conducted interviews following semistructured interview guides and observations following a structured observation checklist (Appendix A1 & B1). We cleaned and coded the data obtained from interview notes. We developed a set of codes and manually sorted data into like-coded blocks of text. We also included descriptive notes and comments from the observations in the analysis.

As part of the interview process, we gave respondents pictures and descriptions of a limited range of vaccine packaging and delivery technologies and we asked for their initial impressions of the technologies' utility in maternal immunization use settings. The purpose of this step was to engage participants in thinking about the impact that packaging and delivery technologies can have on their work environment, productivity, and operations. It also served as a preliminary (but nonspecific) measure of the acceptability and general feasibility of select technology classes that would be likely candidates for pairing with maternal vaccines.

Contextual inquiry took place at the point of maternal immunization delivery—in hospitals, clinics, and other settings where ANC services are provided—to gain a deeper understanding of where the vaccines would ultimately be delivered, the levels of infrastructure available, material and human resources available, who receives the vaccines, and the motivations of the various actors in these environments of use. These details often inform product design decisions and also provide key insight into the ultimate drivers of vaccine coverage—access to the target population and desire (self-motivated or enforced) of the target population to be vaccinated.

Out of scope

Prior to initiating data collection, we excluded from our assessments two topics commonly cited as key barriers to achieving optimal maternal immunization coverage: (1) patient/provider awareness and (2) vaccine cost and procurement issues. While each of these issues will be critical to the ultimate success of new and underused vaccines, the purpose of this assessment was to identify operational barriers that may be addressed by novel packaging and delivery technologies, such as those related to user needs, patient acceptability, and operational fit considerations. While cost and procurement issues are directly related to the ultimate uptake of new packaging and delivery technologies, these issues require a more in-depth and device-specific analysis than can be completed in a formative needs assessment.

Results

Respondents

Key stakeholder interviews

In total, we conducted 16 key stakeholder interviews (5 in South Africa and 11 in El Salvador) with participants who were selected based on their level of expertise and specific knowledge related to maternal and neonatal health in the areas of procurement of vaccines, policymaking, and program and clinic management. These individuals represented a cross-section of key decision-makers as well as

programmatic staff who were active in maternal vaccination from the national Department of Health in South Africa and the Ministry of Health in El Salvador.

Contextual inquiry at health facilities

We conducted contextual inquiry at 11 facilities in South Africa and 9 in El Salvador. In both countries, the sites represented a range of facility levels and services provided. At each facility, we selected a convenience sample of providers from among the ANC health care workers who worked at the participating clinics at the time of the site visit. In total, we interviewed 18 providers in South Africa and 38 providers in El Salvador.

Programmatic constructs and scenarios of maternal vaccine delivery

In both countries, maternal vaccination most frequently occurs at primary health clinics, where all basic health services are provided. The respondents at the clinics spanned the range of types of providers and levels of education, from doctors (in El Salvador only) to registered nurses (diploma) or enrolled nurses (two-year certificate), as well as community health workers. In El Salvador, clinics are staffed primarily by doctors and nurses, with community health workers serving as ancillary staff. In South Africa, clinics are staffed primarily by nurse-midwives (four-year diploma) and community health workers.

The vaccine supply chains and maternal immunization schedules are notably different between South Africa and El Salvador. In South Africa, the supply chains for tetanus toxoid (TT) vaccine, inactivated influenza vaccine (IIV), and childhood Expanded Programme on Immunization (EPI) vaccines differ considerably. However, ultimately, all maternal and EPI vaccines are managed by the provincial head office of the Medical Supply Division. In general, TT is the only vaccine routinely given to pregnant women during ANC visits, although IIV is supplied in limited quantities, seasonally, to clinics. IIV is supplied to facilities in a push mechanism, forecasted at the central level, and distributed through a separate supply chain. Facilities can request more IIV if they run out, but such requests are not always fulfilled. Unlike the IIV vaccine, maternal TT vaccine is procured using a pull mechanism, with facilities submitting regular supply requests to the Department of Health. This pull procurement mechanism for tetanus-containing vaccines involves separate supply tracking and ordering from the childhood EPI pull procurement mechanism. However, at the ANC clinic, maternal vaccines are stored in the same refrigerator as the EPI vaccines, although they are clearly marked for ANC use and stored “separately” inside the refrigerator.

In contrast, El Salvador manages all vaccines under its EPI procurement mechanism. Maternal vaccines are supplied alongside childhood vaccines and are included in the EPI supply chain. The maternal vaccination schedule in El Salvador includes IIV during seasonal campaigns; tetanus, diphtheria (Td) vaccine; and tetanus, diphtheria, pertussis (Tdap) vaccine. Vaccines are forecasted and purchased by the Ministry of Health at the national level based on national-level projections. Forecasting is based on the official estimated population calculated from the last census that was conducted in 2009. The national vaccination manager forecasts for a 15-month supply, factoring in existing stock and expected wastage. El Salvador only procures vaccines and related supplies from the Pan American Health Organization Revolving Fund. Vaccines arrive in the national cold room, are then distributed to the five regions of the country, and from there are distributed to health facilities.

Both countries have experienced stockouts of vaccine: In South Africa, respondents reported that IIV would run out before the conclusion of the influenza season. In El Salvador, respondents reported stockouts of Tdap due to resupply issues. The specifics of vaccine supply and management for each country are described in the corresponding reports (see Annexes 2.1 and 2.2).

Constraints and needs to optimize access to maternal immunization

Through the needs assessments, we identified five categories of constraints:

1. Patient loads
2. Limited cold chain.
3. Limited sharps disposal.
4. Variable training.
5. Access limitations.

Below are descriptions of the manifestations of these constraints and proposed technology needs that could aid in mitigating the constraint.

1. Patient loads

Excessive patient volumes were common problems among ANC providers in both countries. In both countries, wait times for pregnant women seeking ANC may be four to five hours, and ANC providers often work a full eight-hour day without a break. The long waits at the health facility might lead to missed opportunities to vaccinate if the clients leave before they have completed the visits. In El Salvador, health care workers spent more than 50 percent of the ANC visit time filling out paper work, so time-saving measures were a priority to most. Respondents in both countries devised strategies to save time. For example, in South Africa, tetanus vaccine is packaged in ten-dose vials. ANC providers would sometimes prepare multiple doses at the beginning of the day and store the prepared syringes in a vaccine carrier with ice packs in the ANC consultation room. This practice can significantly increase wastage when any unused syringes are discarded at the end of the day. The practice of prefilling syringes from a multidose vial, while common, breaks with the World Health Organization's safe injection recommendations.[2]

Notably, although some novel delivery technologies are designed to have lower training requirements than needle and syringe injection (through increased ease of use and safety), participants in South Africa were reluctant to endorse allowing shifting the task of administering maternal vaccines to community health workers. This may have been due to the difference in the level of training received by community health workers (or enrolled nurse auxiliaries, in some situations) in South Africa versus in El Salvador. In South Africa, these individuals were not trained, and were not perceived as qualified, to manage vaccine delivery. In El Salvador, they were specifically trained to deliver vaccines and were a valued part of the immunization delivery structure.

- Need: Vaccine packaging and delivery technologies that can reduce the amount of time it takes to prepare and deliver a vaccine.
- Need: Vaccine packaging and delivery technologies that can enable task-shifting to lesser-trained providers, where aligned with country policy, clinic flow, and outreach strategy.

2. Limited cold chain

Vaccine vial monitors

In both countries, the vaccines used in maternal immunization (TT for South Africa; IIV; tetanus, diphtheria; and Tdap for El Salvador) did not come packaged with a vaccine vial monitor (VVM) to note when the vaccine should no longer be used due to heat exposure. In El Salvador, the PATH researchers noted that checking for a VVM or other expiry indication (date, shake test) was not done with any vaccines, including those used for EPI; in fact, checking VVMs was not part of the policy or training for vaccinators in El Salvador. This practice increases the risk of damaged vaccine being given to ANC clients.

Figure 1. Inactivated influenza vaccine and tetanus, diphtheria, pertussis vaccine in multidose vials without vaccine vial monitors.

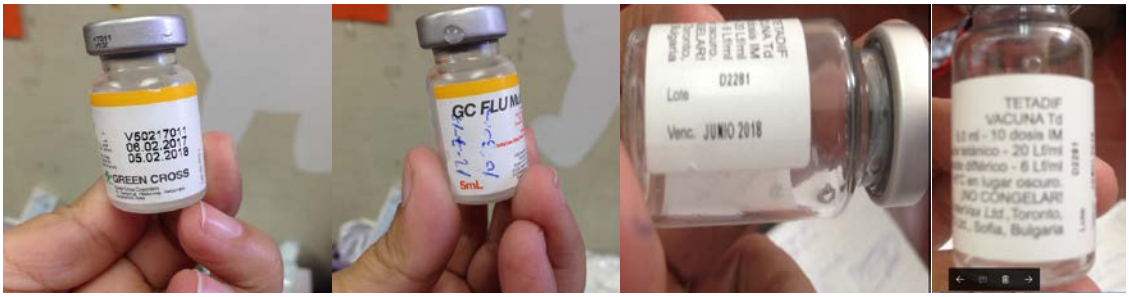

Photo: PATH/Elner Crespin

Cold chain equipment

As is common practice in many EPI settings, the majority of ANC providers at the facilities in both countries in this assessment relied on vaccine carriers to store vaccines in ANC rooms throughout the day; they returned unused doses to the refrigerator in the evenings. In both countries, most of the vaccine carriers, and some of the vaccine refrigerators at the clinics, did not have thermometers to track the temperature range. In El Salvador, there is no budget for regular cold chain strengthening and the Ministry of Health relies on donations of equipment by international organizations. There is also limited budget for maintenance of cold chain equipment, which is limited to correcting problems and does not include preventative maintenance. For example, some respondents noted that they did not have sufficient temperature indicators for monitoring storage conditions. Finally, in El Salvador, there are gaps in the centrally managed distribution network for transporting vaccines under controlled conditions. Each region funds its own distribution transport separately, and this aspect is not rigorously supervised. The national level will assist with vaccine transport if a region requests assistance. Below the regional level, if regional-funded transport is not available, clinic staff will use their personal vehicle to transport vaccines back to facilities. Outside of a temperature-controlled vehicle, this practice risks exposing batches of vaccine to temperature excursions.

- Need: Vaccine and packaging delivery technologies that can allow more flexibility in the cold chain, for example, by enhancing thermostability to ensure that deviations from the temperature range of 2°C to 8°C do not damage vaccine.

3. Limited sharps disposal

In South Africa, clinics routinely had proper sharps waste disposal containers, but participants noted that the smaller containers would often overfill before replacements arrived. This resulted in unsafe disposal conditions. In addition, the sharps containers observed in South Africa were two-part plastic containers

5 L sharps container in South Africa
Photo: PATH/Gwen Ambler

that required assembly before they could be used. Multiple sites reported that they had stockouts of usable sharps containers when the wrong lid size had been supplied, which rendered the container not functional.

In contrast, in El Salvador, many of the facilities visited during this assessment did not have proper sharps waste containers. Instead, they improvised with empty hard plastic bottles, in which they deposited needles. Other facilities had standard cardboard safety boxes. Respondents noted that in order to discard the needle they were trained to recap the needle by a single-hand technique, although this is not in the Ministry of Health guidelines on safe injection practices. In most facilities observed, there was limited clear work-surface area. This left restricted space for performing the recap technique, which could introduce the added risk of needlestick injury. Likewise, at the community level in El Salvador, community health workers reported that the limited space to securely place their supplies has required that they hold everything on their person while preparing and delivering maternal vaccines. This awkward necessity has resulted in reports of needlestick injuries.

- Need: Vaccine and packaging delivery technologies that eliminate or reduce the amount of sharps and glass vials.

4. Variable training

In addition to the understaffing of health facilities, staff retention and training were identified as constraints in both countries. Perceptions as to how to handle these difficulties varied by country. In South Africa, there is a mandatory two-year period of public-sector service for medical professionals once they graduate, but often after those two years, staff seek more lucrative employment in the private sector. As a result, there is frequent need for retraining. In El Salvador, some facilities rotate nursing staff frequently (every few months) among the different services or responsibilities, and refresher training is not always provided. This can result in lost skills among the health workers and missed opportunities for training on new vaccines or delivery methods.

- Need: Vaccine packaging and delivery technologies that require minimal training of health workers and that health workers can be trained on, in a peer-to-peer format.

5. Access limitations

Violence

In El Salvador, violence in specific geographic areas limits both women's access to nearby health facilities and health workers' access during outreach services. This was the barrier that was most commonly noted and usually the first mentioned by the majority of participants; it is a problem faced in many countries with ongoing conflict and violence. In addition, some women work/live outside their usual home area for several months in peri-urban areas. During this time, they may not access ANC or have records of their prior ANC visits. In these cases, community-based volunteers who can offer basic services could provide a needed bridge between the patient and the health system.

- Need: Vaccine packaging and delivery technologies that can enable task-shifting to lesser-trained providers. In these cases, community-based volunteers who can offer basic services could provide a bridge between the patient and the health system.

Transportation limitations

The problem of limited availability of transportation to bring clients to facilities, which necessitates the use of community health workers, also affects health workers who go to the field during vaccination campaigns and to distribute vaccines. Particularly in El Salvador, where there is no practical budget allocated for fuel and vehicle maintenance, health care workers who go to the field must take public transportation. Community health worker respondents in El Salvador complained of neck and back pain associated with the weight of carrying supplies with them all day. They also reported being in instances in which the carrier may be dropped in a crowded bus, which would result in lost doses due to breakage. In addition, they are personally responsible for lost or damaged vaccine and drugs during their outreach sessions.

- Need: Vaccine packaging and delivery technologies that minimize the weight and bulk of supplies.
- Need: Vaccine packaging and delivery technologies that have robust packaging that will not break.

Rightsizing dose per container

Similar assessments of EPI vaccinators' practices have identified the misalignment of vial sizes and patient flow as a barrier to access. This was noted as well in El Salvador and South Africa, particularly related to community-based ANC services.[3] As was noted under the section titled, "Limited cold chain" multidose vaccine vials are routinely at risk of unknown damage due to temperature excursions during storage in vaccine carriers without adequate temperature monitoring or VVMs to indicate cumulative exposure to heat. Maternal vaccines that may become available in the future would likely only be available in single-dose presentations and could not be packaged in multidose vials unless they have preservatives. While single-dose vials enable matching supplies to session size, they increase the volume needed for transportation, storage, and disposal.

- Need: Vaccine packaging and delivery technologies that enable health care workers to rightsize the doses that they take based on the number of expected patients, without having to carry more than is needed.

Provider perceptions of novel delivery technologies

In general, participants found most of the technology concepts useful and interesting. In both countries, fast-dissolving tablets and microarray patches were of particular interest to participants. The single-dose format of these technologies would allow providers to remove a day's worth of doses from the main storage area and return them at the end of the day. Respondents appreciated the potential cold chain flexibility of fast-dissolving tablets and microarray patches. In addition, ease of use and assurance of the correct dose were appealing features of these products. In South Africa, respondents also noted that compact, prefilled, autodisable syringes would have the same advantages. In El Salvador, disposable-syringe jet injectors were included in the top-three preferred technologies for their potential to reduce the pain of injection, increase acceptability among clients, reduce sharps waste, and improve ease of use.

Concerns over the cost of a new technology dominated commentary about disadvantages, and some participants noted that novel packaging and delivery technologies might require specialized training.

Discussion

The constraints identified during the two country-based assessments in South Africa and El Salvador can be distilled into a set of 12 needs relevant to packaging and delivery technologies (Table 1). As stated above, the constraints and related needs reflect health workers overburdened by high patient volumes, cold chain and sharps disposal limitations, variable levels of skill and training, and barriers to access. By identifying the specific needs that are associated with these constraints, the constraints can then be mapped to packaging and delivery technologies that can best address them. This will help to identify those packaging and delivery technologies with the greatest the programmatic feasibility and potential for greatest impact.

Table 1. Constraints identified through needs assessment.

Constraints	Description	To address constraints, health care workers need a packaging/delivery technology that can:
Patient load	Excessive patient volumes. Long wait times can result in loss to follow-up. Improvised time-saving measures, like prefilling syringes (which is against policy). Dose-tracking and dose-scheduling challenges.	Reduces preparation time (the time it takes to prepare the vaccine prior to administration). Reduces delivery time (the time it takes to administer the vaccine, once it is prepared for delivery). Enables task-shifting to minimally trained health workers. Optimizes dose per container: Enables EPI stakeholders to rightsize the doses per container according to the target environment of use
Limited cold chain	Use of vaccine carriers to store daily supplies can result in accidental temperature excursions. Insufficient thermometers or other temperature indicators to ensure appropriate temperature conditions. Transportation challenges can exacerbate cold chain limitations. Vaccine vial monitors are not used consistently on all vials and are not consistently checked.	Increases thermostability to enhance cold chain flexibility and prevent vaccine damage during temperature excursions.
Limited sharps disposal	Usable sharps containers are not consistently available in antenatal care rooms to properly dispose of sharps waste. Community health workers who provide home-based care must give injections while juggling all their supplies, which can increase needlestick injury risk.	Reduce sharps waste. Minimizes weight and bulk of supplies that community health workers need to transport to villages.

Variable training	High staff turnover and/or duty rotation results in varying levels of training and missed opportunities for refresher training.	Minimize training/literacy requirements. Enable task-shifting to minimally trained health workers.
Access limitations	Community health workers have to carry heavy vaccine carriers and supplies with them to the community via public transportation to administer vaccines.	Optimizes dose per container: Enables EPI stakeholders to rightsize the doses per container according to the target environment of use. Reduce glass waste. Minimize weight and bulk of supplies that community health workers need to transport to villages. Ensure robust packaging to prevent damaged/broken supplies.

Conclusion

In spite of differing ANC settings, supply chains, and program structures, South Africa and El Salvador shared several common barriers to achieving optimal maternal vaccination safety and coverage that can be mitigated by novel packaging and delivery technologies. Challenges with patient load were most evident in both countries and were most often referenced by respondents during interviews. Technologies that can improve ease of use and increase speed of vaccine preparation and delivery could address this high-priority constraint. Issues with the cold chain, particularly inconsistent use of VVMs and insufficient temperature monitoring, threaten vaccine effectiveness. This could be mitigated with presentations that offer greater thermostability and enable more flexible cold chain practices. Sharps disposal difficulties can be mitigated by needle-free delivery formats. Variations in the qualifications and training of staff can be addressed by easy-to-use formats that require minimal training and control for critical risk factors such as dosing and injection technique. The needs identified through this process will aid in identifying optimal packaging and delivery technologies for high-priority maternal vaccines.

References

[1] PATH. *Maternal Immunization: Country Priorities and Market Requirements*. Seattle: PATH; 2015. Available at http://www.path.org/publications/detail.php?i=2605.

[2] World Health Organization (WHO). Module 5: Managing an immunization session. In: *Immunization in Practice: A Practical Guide for Health Staff—2015 Update*. Geneva: WHO:17. Available at http://www.who.int/immunization/documents/IIP2015_Module5.pdf?ua=1.

[3] John Snow, Inc. What is the optimal number of doses per vaccine vial? Presented at: TechNet Conference 2015, May 11–15, 2015; Bangkok [poster presentation]. Available at: http://www.slideshare.net/jsi/jsi-technet-poster-optimal-doses-per-vial.

South Africa Maternal Immunization Needs Assessment: Summary of Results

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Contents

Abbreviations

ANC	antenatal care
CPAD	compact, prefilled, autodisable device
EPI	Expanded Programme on Immunization
FDT	fast-dissolving tablet
HIV	human immunodeficiency virus
ID	intradermal
IIV	inactivated influenza vaccine
MAP	microarray patch
TT	tetanus toxoid

Introduction

The development of new vaccines specifically for use in pregnancy, such as Group B *Streptococcus* and respiratory syncytial virus, and expanding the licensure of existing vaccines to include use in pregnancy is becoming an innovation arena with potentially high public health impact. Likewise, understanding where coverage and uptake of existing maternal vaccines could be improved by pairing them with novel packaging and delivery technologies can also contribute to improved maternal and newborn health outcomes. It will be important to have a detailed understanding of the relationship between the operational requirements for maternal vaccines, programmatic priorities of countries introducing them, and which product presentations will be most appropriate for the target settings for use.

To this end, PATH has undertaken a needs assessment in two countries, in settings where maternal vaccines are, or could be, given. The goal of this activity is to determine possible barriers to optimal maternal vaccine coverage that can be addressed by novel and innovative packaging and delivery technologies for these vaccines. In 2016, we completed data collection in South Africa, which was identified during phase 1 of this project as a country with a robust maternal vaccination strategy and a range of types of delivery environments, making the country an optimal location for a needs assessment of this type.[1] In 2017, we conducted a similar assessment in El Salvador, which offers a unique perspective into the challenges faced in a Latin American country struggling with the Zika epidemic. This document presents a summary of the data collected in South Africa.

Methods

We conducted this needs assessment using in-depth key stakeholder interviews with maternal immunization and antenatal care (ANC) experts, and contextual inquiry at health facilities, where we observed service delivery and conducted loosely structured interviews with health care workers who provide maternal vaccinations.

Key stakeholder interviews

We conducted a total of five key stakeholder interviews with participants who were selected based on their level of expertise and specific knowledge related to maternal and neonatal health in the areas of procurement of vaccines, policymaking, and program and clinic management. These individuals represented a cross-section of key decision-makers, as well as programmatic staff from the national Department of Health who are active in maternal vaccination in South Africa.

Contextual inquiry at health facilities

Contextual inquiry includes observation of the informant in his or her own environment, combined with targeted questioning or interviews based on the observations of the qualitative researcher. We conducted contextual inquiry at 11 facilities in two provinces, representing a range of facility levels and services provided. Ten were public-sector facilities, and one was in the private sector (eight private-sector facilities were approached, but only one participated in the assessment). A convenience sample of 18

health care providers was selected among the health care workers working at the participating clinics at the time of the site visit. We conducted contextual inquiry at the point of maternal immunization delivery—in hospitals, clinics, and other settings where ANC services are provided—to gain a deeper understanding of where the vaccines would ultimately be delivered, the levels of infrastructure available, material and human resources available, who receives the vaccines , and the motivations of the various actors in these environments of use. These details often inform not just product design decisions, but they also provide key insight into the ultimate drivers of vaccine coverage—access to the target population and desire (self-motivated or enforced) of the target population to be vaccinated.

Out of scope

Prior to initiating data collection, we excluded from our assessment two topics commonly cited as key barriers to achieving optimal maternal immunization coverage: (1) patient/provider awareness and (2) vaccine cost and procurement issues. While each of these issues will be critical to the ultimate success of new and underused vaccines, the purpose of this assessment was to identify barriers that may be addressed by novel packaging and delivery technologies, such as those related to user needs, patient acceptability, and operational fit considerations.

Results

Five key stakeholders at the national and district levels participated in in-depth interviews. These individuals were experts in maternal immunization and antenatal care at the national and provincial health department levels; they included department of health administrators and program immunization coordinators. In addition, 11 facilities providing ANC services were included in the contextual inquiry component of this assessment (Table 1).

Table 1. Health care facilities visited for contextual inquiry in South Africa.

	Location	Sector	Setting	Number of interviews
	North West Province			
1	Bapong Community Health Centre	Public	Rural, Secondary	1
2	Brits District Hospital	Public	Urban, Tertiary	2
3	Jericho Clinic	Public	Rural, Primary	1
4	Letlhabile Community Health Centre	Public	Peri-urban, Secondary	2
5	Haartebeastspoort Mobile Clinic	Public	Rural, Village	2
	Gauteng Province			
6	Johan Heyns Community Health Centre	Public	Urban, Secondary	2
7	Sharpeville Community Health Center	Public	Peri-urban, Secondary	2
8	Boibatong Community Day Center	Public	Peri-urban, Primary	1
9	Sebokeng Hospital	Public	Peri-urban, Tertiary	3
10	Levai Mbatha Community Health Centre	Public	Peri-urban, Secondary	1
11	Morningside Clinic (Johannesburg)	Private	Urban, Primary	1

Of the facilities visited, maternal vaccination most frequently occurred at primary health clinics, where all basic health services were provided. South Africa currently recommends tetanus toxoid (TT) vaccine and inactivated influenza vaccine (IIV) for use during pregnancy. The 18 respondents were either registered nurses (diploma) or enrolled nurses (two-year degree); all provided a range of health services, including ANC, well-child services, and administration of Expanded Programme on Immunization (EPI) vaccines. At some facilities, nurses provided all types of patient care each day, while at other facilities, EPI and ANC services were provided on alternating days. However, respondents in all facilities were very clear that a woman should never be asked to return for an ANC visit; any time a pregnant woman arrives at the facility, she should be provided with ANC.

The supply chains for TT vaccine, IIV, and childhood EPI vaccines differ considerably. However, ultimately, all maternal and EPI vaccines are managed by the provincial head office of the Medical Supply Division. In general, TT is the only vaccine routinely given to pregnant women during ANC visits, although IIV is supplied in limited quantities, seasonally, to clinics. Many respondents noted that IIV supplies often run out well before the end of flu season. IIV is supplied to facilities in a push mechanism, forecasted at the central level, and distributed through a separate supply chain. Facilities can request more IIV if they run out, but such requests are not always fulfilled. Unlike the IIV vaccine, maternal TT vaccine is procured using a pull mechanism, with facilities submitting regular supply requests to the Department of Health. This pull procurement mechanism involves separate supply tracking and ordering from the standard EPI pull procurement mechanism for tetanus-containing vaccines. However, at the ANC clinic, maternal vaccines are stored in the same refrigerator as the EPI vaccines, although they are clearly marked for ANC use and stored “separately” inside the refrigerator.

Barriers to maternal immunization

Contextual inquiry and interviews with stakeholders highlighted four major barriers related to vaccine supply and delivery that will impact the ultimate scale-up of maternal vaccination in South Africa:

1. Patient load: Time-saving measures are incredibly valuable to staff, and alignment of vaccine vial sizes with patient loads can reduce wastage.
2. Limited cold chain: ANC providers draw supplies from the EPI cold chain and store them in vaccine carriers for use throughout the day.
3. Limited sharps disposal: Usable sharps containers are not consistently available in ANC rooms.
4. Variable training: High staff turnover results in varying levels of training.

Patient load

Excessive patient volumes are common problems among ANC providers, particularly at public facilities. Wait times for pregnant women seeking ANC may be up to five hours, and ANC providers often work a full eight-hour day without a break. Administering maternal immunizations requires several steps for preparation and disposal. For example, in South Africa, TT vaccine is packaged in ten-dose vials, so ANC providers must prepare the correct dose, which may present challenges related to training (see Variable training section). For time efficiency, some providers prepare multiple doses at the beginning of the day and store the prepared syringes in a vaccine carrier with ice packs in the ANC consultation room. Any

unused syringes are then discarded at the end of the day, potentially increasing wastage. The practice of prefilling syringes from a multidose vial, while common, breaks with the World Health Organization's safe injection recommendations.[2]

Novel delivery technologies could help alleviate challenges related to patient load. Technology characteristics that could help improve access to maternal immunization include a single-dose format, potentially more flexible cold chain requirements, and ease of delivery would save time, ensure correct dose measurement, and prevent wastage. Fast-dissolving tablets (FDTs); compact, prefilled, autodisable syringes; and microarray patches (MAPs) would be especially appropriate for busy clinics.

Limited cold chain

As is common practice in many EPI settings, the majority of ANC providers at the facilities in this assessment relied on vaccine carriers to keep the vaccines available in consultation rooms for ANC visits. These carriers are not self-cooling, and only some were observed with thermometers to track the current temperature in the carrier (no temperature indicators other than thermometers were observed). In addition, the TT vaccine vials dedicated for use in maternal vaccination did not come labeled with a vaccine vial monitor to note when the vaccine should no longer be used. Without a temperature indicator to track past temperature excursions, there is increased risk of heat- or freeze-damaged vaccine being given to ANC clients.

Photo: PATH/Gwen Ambler

5 L sharps container

When discussing various novel delivery technologies, participants were especially keen on technologies that may enable cold chain flexibility, such as FDTs and MAPs. These presentations may allow for use of a controlled temperature chain approach, eliminating concerns related to unmonitored temperature deviations once vaccine is removed from the refrigerator. They also have the potential advantage of being packaged in a single-dose format, which would allow providers to remove a day's worth of doses from the main storage area without separating the vaccine from its label and vaccine vial monitor, as the current practice of prefilling syringes does.

Limited sharps disposal

Two sizes of sharps containers, 5 L and 10 L, were observed in the ANC clinics, with the majority of nurses using the 5 L. Participants noted that the 5 L container generally fills up in a couple of weeks, often before resupplies arrive, resulting in stockouts. In addition, the sharps containers observed in this assessment were two-part plastic containers requiring assembly before they could be used. Multiple sites reported that they had stockouts of usable sharps containers when the wrong lid size had been supplied, rendering the container not functional.

Photo: PATH/Gwen Ambler

Vaccine carriers at a clinic pharmacy, ready to be packed.

HIV prevalence in these districts is exceptionally high among ANC clients; one clinic reported that 60 to 70 percent of their clients are HIV positive (obtaining official data on HIV prevalence at this site was out of scope for the evaluation). Serving this population, the risk of infection due to needlestick injury could be quite high in this setting. Multiple interviewees said that needle pricks do happen, although they did not note specific HIV-related precautions or post-exposure prophylaxis steps taken as a result. In previous studies of needlestick injury rates in South Africa, the rate of exposure has been estimated at more than 18 percent, while the lifetime risk of exposure to an individual health care worker has been estimated at roughly 70 percent.[3,4]

FDTs (for sublingual delivery) and MAPs could eliminate the requirement of needle and syringe for delivery of vaccines; respiratory delivery and disposable-syringe jet injectors could serve this purpose for liquid vaccines. Use of integrated reconstitution technologies for lyophilized vaccines would also reduce use of needle and syringes. All of these would reduce the risk of HIV exposure to nurses and would reduce the procurement burden of replacing sharps disposal containers quite as frequently.

Variable training

In addition to having appropriate staff levels, retention and training were identified as necessary for ensuring a skilled workforce. South Africa requires a mandatory two-year period of public-sector service for medical professionals once they graduate, but often after those two years, staff seek more lucrative employment in the private sector—especially in urban areas. As a result, there is frequent turnover among nurses and the need for retraining. Vaccine delivery technologies that could reduce the training burden would save money and also take staff out of the clinic for fewer training hours. Additionally, whenever a new vaccine is introduced, the success of its implementation hinges on the ability of the workforce to be efficiently and effectively trained.

Respondents noted that simplifying vaccine administration could reduce training requirements for each delivery technology. Respondents were particularly interested in the potential of intradermal (ID) adapters, FDTs, and compact, prefilled, autodisable syringes because they all use very familiar administration routes, so the learning curve for a new user was perceived as quite manageable. Although the MAP and disposable-syringe jet injector were not familiar delivery mechanisms, their simplicity appealed to nurses. However, for both of these technologies, participants noted that training requirements may still be substantial. For MAPs, the concept of quick delivery of a vaccine through a patch would be new to most nurses. They would have to clearly understand the differences between hormonal patches that are worn for extended periods of time and vaccine MAPs. In addition, training would have to be comprehensive enough to be able to provide effective patient education to combat misperceptions about patches, as some patients perceive contraceptive patches as causing harmful side effects.

Although ID delivery is not currently used for maternal vaccines, the respondents were familiar with this delivery route for administration of bacille Calmette-Guérin vaccine for tuberculosis. They described the ID adapters as appealing because they could lessen the training requirements needed to learn how to administer ID injections, a technique that takes skill to master. ID delivery technique can affect vaccine effectiveness; if maternal vaccines are developed for the ID route, advance planning to ensure training on correct ID injection techniques or pairing with ID adapters or other novel delivery technologies may have broad impact on the overall success.

Notably, although some novel delivery technologies may have lower training requirements (due to increased ease of use and safety), participants in this assessment were reluctant to endorse allowing

additional cadres of workers to administer maternal vaccines. Community health workers (or enrolled nurse auxiliaries, in some situations) were not perceived as qualified to manage vaccine delivery.

Conclusion

The maternal immunization strategy in South Africa is fragmented by differing vaccine-specific procurement mechanisms, overburdened health care providers, and clinic-based storage patterns that are optimized for EPI services but may not be suited to ANC services. South Africa's network of trained nurses provide ANC services as well as EPI services, resulting in a core clinic team of highly skilled vaccinators providing all maternal and child immunizations. This has the advantage of ensuring that providers who deliver maternal vaccines remain in practice for delivering all vaccines, but it may spread labor too thinly among all the services offered at a given clinic, increasing the risk of mistakes. Moreover, high rates of turnover result in substantial rotating, and retraining, of staff. New and underused maternal vaccines may achieve optimal coverage when paired with novel delivery technologies that can offer time savings, cold chain flexibility, ease of use, low training requirements, and minimal safety risks to patients and nurses. Overall, participants in this needs assessment expressed a high degree of interest in having access to novel delivery technologies for addressing challenges in delivering maternal immunizations in South Africa.

References

[1] PATH. *Maternal Immunization: Country Priorities and Market Requirements*. Seattle: PATH; 2015. Available at: http://www.path.org/publications/detail.php?i=2605.

[2] World Health Organization (WHO). Module 5: Managing an immunization session. In: *Immunization in Practice: A Practical Guide for Health Staff—2015 Update*. Geneva: WHO:17. Available at http://www.who.int/immunization/documents/IIP2015_Module5.pdf?ua=1.

[3] Kruger WH, Oluwatosi Jimoh S, Joubert G. Needlestick injuries among nurses in a regional hospital in South Africa. *Occupational Health Southern Africa.* 2012;18(3):4–10.

[4] Delobelle P, Rawlinson JL, Ntuli S, Malatsi I, Decock R, Depoorter AM. HIV/AIDS knowledge, attitudes, practices and perceptions of rural nurses in South Africa. *Journal of Advanced Nursing*. 2009;65(5):1061–1073.

Researcher Initials	**Facility ID**

Facility-Specific Questions

To be used by researchers to record observations about the facility in which the evaluation is taking place.

1. In a typical day, how many staff are at this clinic? What roles do they have? PROMPT: SUPERVISORS, COWORKERS, PATIENTS/CLIENTS, OTHER?
2. How often do you feel the work load is too busy for the available staff?
3. How many ANC clients do you typically see in a day? In a week? Are some days busier? How busy? Why?
4. What is the average socioeconomic status of the clients who visit this facility? Are most literate?

Facility infrastructure:

1. How often are blackouts? Is there a backup generator?
2. How many refrigerators are you using right now? What size? Is there enough space in these?
3. What do you keep in the refrigerator/s? Are any refrigerators reserved for specific purposes? Which purpose? Where are they located?

Facility Observation Checklist

- Note ambient temp
- Note humidity (High / Med / Low)
- Note lighting conditions (is there electric lighting? Is it on at time of observation?)
- Note building structure (what is size/layout/indoor or outdoor spaces used/construction materials?)
- Note the number of rooms where ANC is provided
- Note the number of trips between rooms during routine activities
- Describe work surfaces (how long is the table? Where is the infant placed?)
- Describe work equipment (fridge, injection supplies, furniture, etc.)
- Describe work tools (devices, safety, gloves, other?)
- Describe work station (+ personal equipment, tools, devices, etc.)
- Describe interactions w/objects in environment
- Describe the typical workflow: where do they start, how long do they take, where do they finish, and what do they use?
- Describe routine communications with people (who? how long?)
- Did user consult reference materials?
- Describe influencers (+/-)—people or actions that impact how work is conducted
- Note any points of friction/frustration in routine tasks
- Describe other items of note

Researcher Initials	**Facility ID**

Facility Observation Notes & Mapping

Draw map of setting (Where is ANC given? HCW station? Patients? Equipment/supplies? Routes between rooms?):

Researcher Initials	Facility ID

HCW Interview Guide

Participant ID:

Background

Explain purpose of the visit and context of maternal immunization. Confirm that the participant is available to answer questions for about 15 minutes, and that there are no patients waiting to be seen by him/her.

1. Please describe your job—what is your job title? What duties do you have? PROMPT: GENERAL CARE, VACCINATION, MANAGEMENT, OTHER?
2. How long have you been doing this job?
3. What professional degrees/certifications do you have?

Experience Giving Maternal Vaccines

4. How often do you give vaccines to pregnant women?
5. Which vaccines do you give to pregnant women?
6. Ideally, if cost were not a concern, what other vaccines and therapies should a pregnant woman receive as part of her general antenatal care?
7. Where do you give vaccines to pregnant women—here at the clinic? At their homes? At community centers? Are there other places where you give vaccines to pregnant women?
8. Do pregnant women coming for ANC ever request vaccines for themselves? How often does this happen?
9. Why do you decide whether to offer a vaccine to a pregnant woman when she visits for ANC?
10. Why do you decide not to give a vaccine to a pregnant woman?
11. What are the biggest challenges that you face for giving a vaccine to a pregnant woman? PROMPT: COLD CHAIN, DISPOSAL, CLEANLINESS, RECORD KEEPING, STORAGE, TRANSPORT TO COMMUNITY LEVEL?

Here are some examples of different ways to deliver vaccines.

12. Which of these delivery devices would you prefer for giving a maternal vaccine? Why?

Researcher Initials	**Facility ID**

Key Stakeholder Interview Guide

Participant ID:

(Prior to interview, collect stakeholder: Job title, professional degrees, general job description)

Background

Explain purpose of the visit and context of maternal immunization.

1. What factors are/will be considered when selecting a maternal vaccine for inclusion in national health services? PROMPT: COST, AVAILABILITY, STABILITY, COLD CHAIN CAPACITY, USABILITY, TRAINING/RE-TRAINING, OTHER, DISPOSAL?
2. What are the steps in the supply chain for maternal vaccine? PROMPT: STARTING FROM SOURCE: GAVI/DIRECT PURCHASE/DONOR. CUSTOMS: PROCESS, DELAYS? CENTRAL STORES: REFRIGERATION, DURATION, ETC. TRANSPORT MODES, DURATION, ETC.
3. Is distribution of maternal vaccines independent of the EPI vaccines, or are they linked to the EPI or other product supply chains, etc.?
4. Currently we understand that maternal vaccines are given in ___ settings. Ideally, are there other settings in which maternal vaccines could be given to improve coverage of vaccination to women during pregnancy?
5. Are there other services—health services, household goods provision, or other commercial services—that would be good for integrating with provision of vaccines to pregnant women?
6. What are the biggest challenges to achieving target coverage of maternal vaccines? PROMPT: COLD CHAIN, DISPOSAL, CLEANLINESS, RECORD KEEPING, STORAGE, TRANSPORT TO COMMUNITY LEVEL?

Here are some examples of different ways to deliver vaccines.

7. Which of these delivery devices would be best for giving a maternal vaccine? Why?
8. Is there anything else we should know about barriers to delivering maternal vaccines?

El Salvador Maternal Immunization Needs Assessment: Summary of Results

SEPTEMBER 26, 2017

Submitted to Pfizer Independent Grants for Learning & Change

Grant #16217821, Improving access to adult vaccines in low-resource settings with novel packaging and delivery technologies

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Contents

Abbreviations

ANC	antenatal care
EPI	Expanded Programme on Immunization
GBS	Group B *Streptococcus*
MINSAL	Ministerio de Salud (Ministry of Health)
PAHO	Pan American Health Organization
RSV	respiratory syncytial virus
SIBASI	Sistema Básico de Salud Integral (Integrated Health Basic System)
Tdap	tetanus, diphtheria, pertussis
VVM	vaccine vial monitor

Introduction

The development of new vaccines specifically for use in pregnancy, such as Group B *Streptococcus* (GBS) and respiratory syncytial virus (RSV) is becoming an innovation arena with potentially high public health impact. Likewise, understanding where coverage and uptake of existing maternal vaccines could be improved by pairing them with novel packaging and delivery technologies can also contribute to improved maternal and newborn health outcomes. It will be important to have a detailed understanding of the relationship between the operational requirements for maternal vaccines, programmatic priorities of countries introducing them, and which product presentations will be most appropriate for the target settings for use.

To this end, PATH has undertaken a needs assessment in two countries, in settings where maternal vaccines are, or could be, given. The goal of this activity was to determine possible barriers to optimal maternal vaccine coverage that can be addressed by novel and innovative packaging and delivery technologies for maternal vaccines. In 2016, we completed data collection in South Africa, which was identified during the work completed under Objective 1 of this project as a country with a robust maternal vaccination strategy and a range of types of delivery environments, making it an optimal location for a needs assessment of this type.[1] In 2017, we conducted a similar assessment in El Salvador with the intention of understanding the unique challenges faced in a Latin American country struggling with the Zika epidemic. This document presents a summary of the data collected in El Salvador.

Objectives

The goal of this needs assessment was to understand the context of use and intersection of antenatal care (ANC) and maternal vaccination programs. The results of this assessment will then inform PATH's work to identify which novel and innovative packaging and delivery technologies could make delivery of maternal vaccines and ANC interventions more efficient in El Salvador and other resource-limited settings.

The objectives of this needs assessment in El Salvador were:

1. Describe the programmatic constructs, scenarios of delivery, ANC and coverage rates of maternal vaccines.
2. Describe constraints and needs for optimizing access to maternal immunizations in ANC settings.
3. Describe provider perceptions regarding administering maternal immunizations and other antenatal preventative therapies.

Out of scope

Prior to initiating data collection, we excluded from our assessment two topics commonly cited as key barriers to achieving optimal maternal immunization coverage: (1) patient/provider awareness and (2) vaccine cost and procurement issues. While each of these issues will be critical to the ultimate success of

new and underused vaccines, the purpose of this assessment is to identify barriers that may be addressed by novel packaging and delivery technologies, such as those related to user needs, patient acceptability, and operational fit considerations.

Methods

We conducted a qualitative needs assessment using document review of country policies, in-depth interviews, and observation at facilities. We interviewed maternal immunization and ANC experts at the regional, national, and local levels, including key stakeholders at the national program level and health workers in ANC and immunization settings. We used purposive sampling to select individuals who were especially knowledgeable about maternal immunization in order to achieve deep understanding of the topic of interest.

We conducted interviews following a semistructured interview guide and conducted observations following a structured observation checklist (Appendix B1). We cleaned and coded data obtained from interview notes. We developed a set of codes and manually sorted data into like-coded blocks of text. We also included descriptive notes and comments from the observations in the analysis.

Results

We visited a total of nine health facilities and one regional cold store[a] during July 2017. Characteristics of health facilities can be found in Table 1. We conducted interviews with 50 participants ranging from national leaders to local providers of maternal health and vaccination programs. Characteristics of participants can be found in Table 2.

Table 1. Characteristics of health facilities visited for needs assessment, El Salvador.

Number	Name of facility	Level of care	Setting	Region	Department	SIBASI
1	Hospital de la Mujer	Tertiary	Urban	Metropolitan	San Salvador	SIBASI Centro
2	Hospital National San Rafael	Secondary	Urban	Central	La Libertad	SIBASI La Libertad
3	UCSF Panchimalco	Primary	Rural	Metropolitan	San Salvador	SIBASI Sur
4	UCSF San Salvador Barrios	Primary	Urban	Metropolitan	San Salvador	SIBASI Centro
5	UCSF Díaz del Pinal	Primary	Urban	Central	La Libertad	SIBASI La Libertad

[a] At the regional cold store visited, refrigerators and freezers were kept in a room with air conditioners, but these were only turned on between 8 a.m. and 3 p.m. because they were not made for continuous use.

Number	Name of facility	Level of care	Setting	Region	Department	SIBASI
6	UCSF Comasagua	Primary	Rural	Central	La Libertad	SIBASI La Libertad
7	UCSF San Salvador Lourdes	Primary	Urban	Central	La Libertad	SIBASI Centro
8	UCSF San Salvador Monserrat	Primary	Urban	Metropolitan	San Salvador	SIBASI Centro
9	UCSF San Salvador San Miguelito	Primary	Urban	Metropolitan	San Salvador	SIBASI Norte

Abbreviations: SIBASI, Sistema Básico de Salud Integral (Integrated Health Basic System); UCSF, Unidad Comunitaria de Salud Familiar (Family Health Community Clinics).

Table 2. Characteristics of needs assessment participants, El Salvador.

Type of participant	Professional and educational background (number interviewed)
National program leaders and managers (experts in maternal health, immunization program, primary care)	Doctors (4)
Metropolitan region managers (experts in maternal health, immunization program)	Doctor (1) Nurses (2)
Metropolitan region storekeepers	Secondary schooling (2)
SIBASI Centro managers (experts in maternal health, immunization program)	Doctor (1) Nurses (1)
Tertiary-level providers (ANC and EPI services)	Obstetrician (1) Nurses (4)
Secondary-level providers (ANC and EPI services)	Obstetrician (2) Nurses (2)
Primary-level providers (ANC and EPI services)	Nurses (14) Doctors (8
Community health workers (ANC and EPI services)	Secondary schooling (7)
Total	49

Abbreviations: ANC, antenatal care; EPI, Expanded Programme on Immunization; SIBASI, Sistema Básico de Salud Integral (Integrated Health Basic System).

Programmatic constructs and scenarios of delivery of ANC, and frequency of administration of maternal vaccines in El Salvador

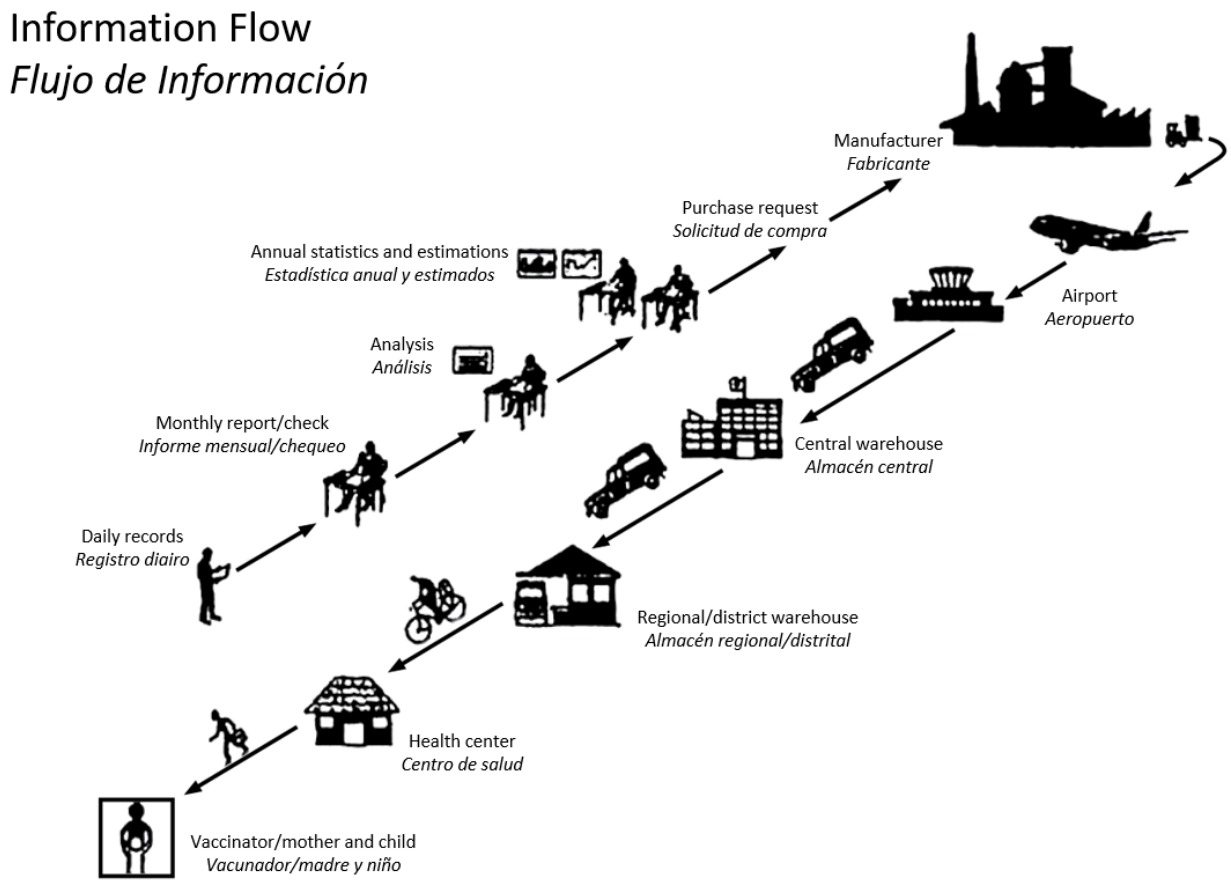
El Salvador's health system structure and vaccine supply chain

El Salvador's health system comprises the Ministerio de Salud (MINSAL or Ministry of Health), Instituto Salvadoreño del Seguro Social (for social security), Instituto Salvadoreño de Rehabilitación a los

Inválidos (for the disabled), Sanidad Militar (for the military), Instituto Salvadoreño de Bienestar Magisterial (for teachers), Fondo Solidario para la Salud (separate government funding mechanism), and private institutions. More than 60 percent of the population receives care from the MINSAL, and less than 20 percent have social security. Health policies are determined by the MINSAL. The MINSAL services are administratively divided in five regions and 17 SIBASI (Sistema Básico de Salud Integral or Integrated Health Basic System). This ensures equitable distribution of health facilities across the country and limits geographical access as a barrier. However, violence in some rural areas limits the ability of some women to seek care in areas controlled by certain criminal groups. This is discussed further in the Constraints section, below.

Maternal vaccines in El Salvador are procured and supplied alongside standard childhood vaccines. Maternal vaccines are included in the Expanded Programme on Immunization (EPI) supply chain. Vaccines arrive in the national cold room, are then distributed to the five regions, and from there are distributed to health facilities. Most regional cold rooms will ask facilities to come pick up their vaccines directly. The exception is the metropolitan region, which typically distributes the vaccine directly to facilities. However, in 20 percent of instances when transportation is not available, the metropolitan regions ask facilities to pick up their doses.

Figure 1. Typical vaccine distribution in the cold chain in El Salvador[2]



Vaccines are forecasted and purchased by the MINSAL at the national level based on national-level projections. Forecasting is based on the official estimated population calculated from the last census that was conducted in 2009. The national vaccination manager forecasts for a 15-month supply, factoring in existing stock and expected wastage. El Salvador only procures vaccines and related supplies from the Pan American Health Organization (PAHO) Revolving Fund.

Outside of vaccines, the only other antenatal supply that all women receive is iron with folic acid (calcium is only provided in high-risk pregnancies). These supplements, along with any other drugs, are forecasted based on prior-year consumption at the regional level and then rolled up at the national level for yearly acquisition. The ANC drug supply chain is managed separately from the cold chain for vaccines; beyond the national level, how cold chain space is allocated varies. In some regions, there is one cold room for vaccines and a separate cold room for drugs, while in others, particularly metropolitan areas, the same room contains separate refrigerators for vaccines and for drugs.

New vaccine and technology introduction in El Salvador

PAHO and CDC play an important role in advocating for the introduction of a new vaccine or technology. The El Salvador Vaccine Advisory Committee (ESVAC) considers such recommendations, looking at the burden of disease, evidence, and experience of other countries. The committee then makes a technical recommendation to the head of El Salvador's infectious disease program who reviews it, taking into account budgetary and other practical considerations, and submits it to the Minister of Health. In the end, the Minister of Health either will approve the recommendation or not based on the technical recommendation and budget available. Any new vaccine/technology must be available through the PAHO Revolving Fund, as it is the only supply mechanism used by the MINSAL.

The last vaccine that was introduced in El Salvador's immunization schedule was the inactivated poliovirus vaccine, based on PAHO's advocacy. In terms of currently available vaccines that are not already part of the El Salvador maternal immunization schedule, dengue vaccine is not being considered, as related mortality in El Salvador is very low and pregnant women have strict monitoring across the health system whenever they have fever. However, Zika vaccine could be considered once there is enough evidence and experience in other countries to demonstrate effectiveness and impact.

Incorporation of a new vaccine delivery technology would require an additional administrative process within the MINSAL. Just like the process for vaccines, the ESVAC would have to propose incorporating the new vaccine delivery technology and the head of the infectious disease program would need to approve it. However, approval would also need to be sought from the Unidad de Insumos y Aparatos (commodities and machines unit), as well as a new entity called Unidad de Vigilancia Tecnológica (technology surveillance unit).

When introducing a new technology or vaccine that is built on a predicate technology, health worker training is a priority. This need was highlighted a few years ago when autodisable syringes were introduced in the country and lack of proper training resulted in high wastage of both vaccines and syringes, as health workers tried to use them as regular syringes.

Levels of the health system

Community-based services

Community health workers have been crucial in expanding coverage of all health services in rural areas. Each week, they visit an average of six to ten communities and 40 to 60 houses. They bring vaccine carriers and supplies to vaccinate the population in those communities twice a week or daily during vaccination campaigns. Typically, they will bring with them more than 20 vaccine vials, including maternal vaccines. On average, they will visit two pregnant women each day, and they will apply several doses of vaccines. ANC is provided free of charge to all pregnant women at all levels of care.

Primary health clinics

Most women without risk factors will be followed in primary care facilities and referred for follow-up to higher levels of care if risk factors are identified. In keeping with this format, most vaccinations are given at the primary care level. As part of this, community health workers are tasked with vaccinating pregnant women in rural areas and with searching for women at home who miss attending their scheduled ANC visit and vaccination. Basic ANC at the primary care level entails five comprehensive ANC visits in which the following processes take place: history taking; breast, pelvic, and vaginal examinations; prenatal blood tests; urine test; pap smear; uterine ultrasound; vaccination; provision of nutrient supplements (folic acid and iron); health education; and nutrition, dentistry, and psychology consultations.

Current coverage for five ANC visits is 90 percent, and most women come for the first time during their first trimester. The first time a pregnant woman comes for ANC at the primary care level, she will spend approximately four hours for the visit. This visit typically includes taking a pregnancy test (if warranted); visiting the facility registry to get her file; getting her vital signs taken by a nurse; getting vaccinated; waiting between appointments; attending an ANC visit with a doctor; getting blood tests; getting counseling from a nurse; attending or scheduling an appointment with a nutritionist, dentist, and psychologist; getting drugs from the pharmacy; and scheduling the next ANC visit at the facility registry. Therefore, a client usually interacts with upwards of five different individuals during the course of her first visit.

Although coverage for five ANC visits is high, coverage for maternal immunization is significantly lower. The maternal vaccination schedule in El Salvador includes[3]:

- Influenza vaccine: During a seasonal campaign, one dose should be provided on the first ANC visit or during a community outreach campaign, regardless of gestational age. Total coverage in 2016 was 50 percent.
- Td vaccine: One dose should be provided during every pregnancy when turning 16 weeks gestational age. If the woman has not received a prior childhood tetanus vaccination, two doses should be provided; ideally, the second dose should be substituted with tetanus, diphtheria, pertussis [Tdap] vaccine). Total coverage in 2016 was 73 percent.
- Tdap vaccine: One dose should be provided during every pregnancy when turning 26 weeks gestational age. Total coverage in 2016 was 39 percent. This lower coverage was attributed to delayed supply of Tdap.

Coverage rates for maternal immunizations are tracked at the national-level immunization program, which tracks coverage for all immunizations—both for children and adults. The lower maternal immunization coverage can be attributed to several factors. In forecasting target populations, respondents had a perception of a mismatch between national vaccine forecasting estimates of the target population of

pregnant women (higher) and the actual target population (lower). Vaccine stockouts can also lead to lower coverage rates, as a woman may not receive the needed vaccine at her visit and may subsequently be lost to follow-up. Lastly, in the case of influenza, not all women forecasted to be pregnant in a year are actually pregnant during influenza vaccine season.

Secondary/tertiary facilities (hospitals)

Women seen at secondary and tertiary level facilities generally have been referred for follow-up due to high-risk pregnancy. In these facilities, the responsibility of checking the completeness of the client's vaccination schedule was not always clear (obstetrician vs nurse), which could lead to delayed or missed vaccination. Just as in a primary care facility, a pregnant woman will go through several interactions during her ANC visit at these facilities, such as obtaining her file from the facility registry, getting her vital signs taken by a nurse, attending an ANC visit with a doctor, among others.

Constraints and needs for maternal immunizations in ANC settings in El Salvador

Programmatic constraints

Attendance of ANC visits is high, but there are still significant constraints to be addressed in El Salvador to optimize coverage. One of the most evident at the time of the assessment was the stockout of Tdap in many facilities. This was primarily due to: 1) delayed payment to the PAHO Revolving Fund (caused by delayed processing by El Salvador's revenue system, which provides budgets to all sectors), and 2) delayed production by the manufacturer. In addition, PAHO's delivery of vaccines may be delayed due to regional supply factors outside of El Salvador's control. For example, one national-level respondent explained that once payment to the Revolving Fund is made, PAHO determines which vaccines will be shipped first. The perception of the national-level respondent was that PAHO views Tdap as a lower-priority vaccine for El Salvador.

In addition, El Salvador's government budgetary plans are made in advance, and each plan is effective for a five-year period of time. The system also has complex administrative processes for supplying vaccines and drugs, so this limits any sudden increase in budget. This could have an impact on the country's ability to respond rapidly to an emerging epidemic.

Limited cold chain

Most respondents in most facilities visited perceived the cold chain capacity to be adequate. During vaccination campaigns (like influenza season), supply chain managers accommodate the additional stocks by increasing the frequency of distribution to facilities. Only the storekeepers from the Metropolitan Region's improvised cold room expressed needing more space and more refrigerators.

There is no budget for regular cold chain strengthening, and the MINSAL relies on donations of equipment by international organizations. Respondents in some facilities noted that their refrigerators were not "official" vaccine refrigerators but rather were ones appropriate for drugs only. There is also limited budget for maintenance of cold chain equipment, which is limited to correcting problems and does not include preventative maintenance. For example, some respondents noted that they did not have sufficient temperature indicators for monitoring storage conditions. Finally, there are gaps in the centrally managed distribution network for transporting vaccines under controlled conditions. Each region funds its own distribution transport separately, and this aspect is not rigorously supervised. However, the national

level will assist with vaccine transport if a region requests assistance. Below the regional level, if program-funded transport is not available, clinic staff will use their personal vehicle to transport vaccines to facilities.

Access limitations

Violence

Violence in specific geographic areas limits both women's access to nearby health facilities and health workers' access to clients during outreach services. This was the most commonly noted and usually the first barrier to access mentioned by the majority of participants. In addition, some women work/live outside their usual home area for several months in peri-urban areas. During this time, they may not access ANC.

Transportation limitations

Delivery has several limitations that would prevent rapid uptake of a new vaccine and that remain a barrier to optimal coverage of the existing maternal vaccines in El Salvador. Some examples of these operational constraints are the challenges faced by community health workers who travel out to villages to offer health services in the home. The same problem of limited availability of transportation to bring clients to the facilities also affects health workers going to the field during vaccination campaigns and routine outreach services. There is no practical budget allocated for fuel and vehicle maintenance, so community health workers going to the field must take public transportation. Community health worker respondents complained of neck and back pain associated with the weight of carrying supplies with them all day. There were reports of instances in which the carrier may be dropped in a crowded bus, which would result in lost doses due to breakage. In addition, community health workers are personally responsible for lost or damaged vaccines and drugs during their outreach sessions.

Human resources

Facilities were often constrained by limited human resources, particularly in basic primary level units. Health care workers spent more than 50 percent of the ANC visit time filling out paperwork, so time-saving measures were a priority to most. Often facilities were missing human resources on-site due to scheduling issues, staff being gone to pick up vaccine stock, or vaccination campaign activities. This resulted in health care workers who felt that they were overloaded with clients—their number of clients was disproportionate to their ability to see them. In addition, patient scheduling did not appropriately factor the number of staff available on a given day or the additional time it takes for the first ANC exam, where the additional registration and counseling requirements extend the length of the visit. The resulting long wait (approximately four hours) at health facilities might lead to missed opportunities to vaccinate if the clients leave before they have completed visits. Finally, policy at each facility dictates that nursing staff rotate frequently (every few months) among the different services or responsibilities, and refresher training is not always provided.

Vaccine vial monitors

In this assessment, vaccine vial monitors (VVMs) were not observed on most vaccine vials in the vaccine refrigerators (for EPI or maternal vaccines), with the exception of oral polio vaccine vials. VVMs were seen on cartons of vaccine but not the vials. According to respondents, only the distributor checks a VVM at the time that the supply is shipped to the country. None of the staff were observed looking for a VVM or checking the expiry date on vaccine vials during routine care. This could be particularly problematic as vaccines are routinely removed from the refrigerator and stored in a vaccine carrier for daily use; then, at the end of the day, vials with remaining vaccine are returned to the refrigerator for subsequent use.

However, vaccinators were observed recording the date and time that the vial was opened, in keeping with multidose vial policy. In one instance, a vaccine carrier was not closed between uses, exposing vaccine to ambient temperatures.

Figure 2. Inactivated influenza vaccine and tetanus, diphtheria, pertussis vaccine in multidose vials without vaccine vial monitors.

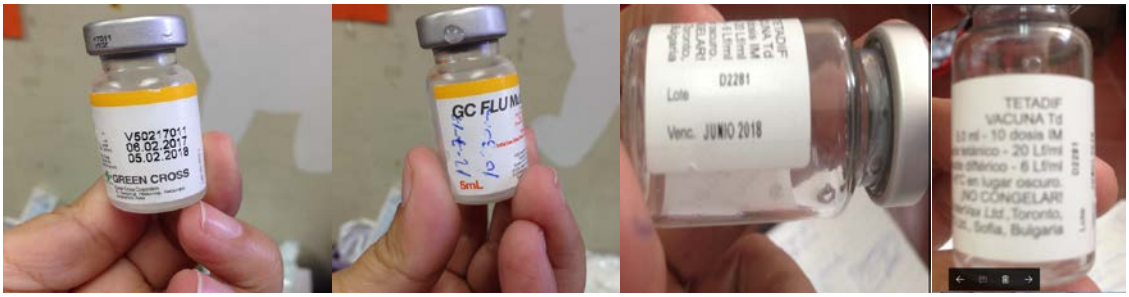


Photo: PATH/Elner Crespin

Photos: PATH

Limited sharps disposal

Many of the facilities visited during this assessment did not have proper sharps waste containers. Instead, they improvised with empty, hard plastic bottles, in which were they deposited needles. Respondents noted that they were trained to recap the needle by a single-hand technique in order to discard the needle, although this is not in the MINSAL guidelines on safe injection practices. In most facilities observed, there was limited space for the vaccine carrier and all the related supplies. This left restricted space for performing the recap technique, which could introduce the added risk of needlestick injury.

Likewise, at the community level, the limited space to securely place supplies has required community health workers to prepare the vaccine dose while carrying everything on their person. This awkward necessity has resulted in reports of needlestick injuries. Community health workers also reported that the handle of the cardboard safety box hurt their fingers when they carried them during outreach services.

Provider perceptions regarding administering maternal immunizations and other antenatal preventative therapies in El Salvador

Although respondents in the assessment had a positive perception of maternal immunization in general, they were still asked what they would change to existing maternal vaccine presentations and what could make their everyday tasks in ANC and maternal vaccination easier. Results are presented below; they have been edited to exclude statements of needs outside the scope of this assessment, such as those related to general provision of ANC services not related to vaccination.

Figure 3. Antenatal care providers' statements of need related to maternal vaccines.

- Vaccine vial labels should be waterproof as they easily come off when they get wet in a vaccine carrier. This can lead to different vaccines looking similar and being easily confused.
- The label color used for a given vaccine should be consistently the same even if they are produced by different manufacturers. Currently, pentavalent vaccine from one manufacturer is blue and from another one it is purple.

- Vaccine vials should come as single dose to avoid the wastage that results from opening multidose vials.
- Vaccine vials should look less alike. Currently, the pentavalent vaccine vial looks like the pneumococcal vaccine vial, and the tetanus-diphtheria adult formulation (Td) vaccine vial looks like the diphtheria, pertussis, and tetanus vaccine vial.
- Vaccines should be given orally.
- Vials should be made of plastic instead of glass.
- Vaccination should not be so painful (Td).

At the conclusion of assessment interviews, respondents received descriptions of different types of vaccine packaging and delivery technologies and were asked for their initial impressions of the technologies' utility in the El Salvador maternal immunization use settings. In general, participants found most of the technology concepts useful and interesting; their main concern about adoption was cost. The majority of participants were particularly engaged by the idea of fast-dissolving tablets, disposable-syringe jet injectors (which are needle-free, a key feature of interest to respondents), and microarray patches. They noted the advantages that the technologies offered in terms of reducing the need for cold chain and storage space, decreasing client pain due to injection, increasing acceptability among the population, decreasing costs associated with delivery supplies, and being easier to use. Besides cost, the other concern expressed by some participants was the need for training, particularly when switching an existing vaccine schedule that may require different doses—for example, from parenteral to oral delivery.

Conclusion

El Salvador's ANC program seems to be quite successful in reaching the majority of pregnant women in the country. However, pregnant women face long waits at the facility and health workers spend a considerable amount of time filling out paperwork.

Maternal vaccination coverage is limited by system challenges related to the timely supply of vaccines and distribution. We identified a high risk of potential cold chain interruptions given the lack of budget for cold chain strengthening, transportation, and maintenance. We also noted the absence of use of VVMs. Since vaccines are used daily and some open vials of vaccine are returned to the cold chain, this could impact vaccine integrity.

Additionally, we also identified a high risk of potential needlestick injuries in health workers given the lack of proper sharps disposal and space constraints both at facility and community levels. Community health workers, who have been key in increasing coverage in rural areas, are also burdened with heavy workloads and lack of transportation.

In terms of vaccine delivery technologies, the health system would benefit from technologies that can withstand an unreliable or flexible use of cold chain, decrease storage and transportation space needed, decrease the need for sharps, avoid use of glass, and are lightweight to carry at the community level.

References

[1] PATH. *Maternal Immunization: Country Priorities and Market Requirements.* Seattle: PATH; 2015. Available at http://www.path.org/publications/detail.php?i=2605.
[2]El Salvador Minister io de Salud. *Lineamientos Técnicos para la Conservación de la Cadena de Frio*. San Salvador: Ministerio de Salud; 2014. Available at http://asp.salud.gob.sv/regulacion/pdf/lineamientos/lineamientos_cadena_frio.pdf.
[3] Sistema Nacional de Registro de Vacunas page. Ministerio de Salud website. Available at http://vacunas.salud.gob.sv/. Accessed August 24, 2017.

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Número de identific | | | | |

GUÍA PARA LA ENTREVISTA CON TRABAJADORES DE SALUD A NIVEL LOCAL

Fecha: _____ Municipio: _____

UCSF: _____

Departamento: _____Zona: _____

I. Perfil de Trabajador de Salud

1.	Género	1. ◯ Hombre 2. ◯ Mujer
2.	Cargo / puesto en la clínica	1. ◯ Promotor de Salud 2. ◯ Enfermera 3. ◯ Medico 4. ◯ Otro:_____
3.	Años de trabajo (total)	
4.	Tipo de estudios obtenidos para el puesto de trabajo (años / grado)	1. ◯ Técnico 2. ◯ Licenciatura 3. ◯ Doctor 4. ◯ Especialista 5. ◯ Otro:
5.	Descripción de un día típico de trabajo	
6.	¿Hay otras responsabilidades laborales que no se realizan todos los días?	1. ◯ Si 2. ◯ No
7.	En caso afirmativo ¿Cuáles?	

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II. Entorno de la APN

8. Por favor describa paso a paso cómo es una consulta típica cuando una madre embarazada viene a su primera cita de APN. (inscripción prenatal)	
Inicio:	
Paso 2:	
Paso 3:	
Paso 4:	
Paso 5:	
Paso Final:	
9. ¿Cuáles otras actividades o intervenciones realiza/administra en las consultas prenatales de APN subsecuentes?	
10. ¿Cuánto dura una consulta en promedio? Primera vez: Subsecuente:	
11. ¿Qué podría prolongar la consulta?	
12. ¿En general, en que trimestre del embarazo se presenta la mujeres embarazadas para su cita de primera vez?	
13. ¿Numero promedio de controles que recibe una mujer embrazada? --(1 a 9 controles) 14. Considera usted que las mujeres en su mayoría acuden o no acuden a recibir por lo menos los 5 controles básicos?	
15. ¿En cuántos consultorios dentro de esta unidad se dan las consultas prenatales?	
16. ¿En qué otras áreas trabaja usted durante el día? (área de urgencia, área de cirugía menor, cuarto de vacunación, área de preparación, etc.)	
17. ¿En qué momento de la visita se le administra la vacuna a la mujer embarazada? (Al llegar con enfermería antes de la consulta APN, o después de la consulta de APN, etc.)	
18. ¿En dónde sucede la vacunación?	1. ◯ Cuarto específico para vacunación 2. ◯ En consultorio improvisado

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.	3. ◯ En el área de preparación 4. ◯ Otra:_____
Los promotores de salud de esta unidad ¿Reciben un termo con biológico para administrar vacuna en la comunidad? ¿Cuál es el procedimiento (a qué hora lo reciben y a qué hora regresan con el sobrante)?	
19. ¿Puedo ver la vacuna que tiene en uso? (anotar si es multidosis / dosis única, fabricante, tomar foto del producto que incluya <u>nombre</u> del biológico, <u>fecha de caducidad y fecha en que fue abierto</u> si es que es multidosis) <Si APN vacuna>	1. ◯ Es multidosis 2. ◯ Es dosis única Nombre del fabricante: _____
20. Permito tomar foto: --- caso afirmativo tomar foto <Si APN vacuna>	1. ◯ Si 2. ◯ No
21. ¿Dónde se almacena los medicamentos prenatales (multivitamínicos, calcio)?	

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ENFERMERA:

22.1 ¿A quién le toca revisar el esquema de vacunación de la embarazada (médico o enfermera)?

¿Quién realmente lo hace siempre?

22.2 ¿Se entregan mosquiteros e insecticida (DEET) rutinariamente a embarazadas?

22.3 ¿En su experiencia, las embarazadas le han comentado si tienen algún problema para tomar el ácido fólico con hierro? En caso afirmativo, ¿De todas formas se toman el medicamento?

22.4 Durante la consulta… ¿Cuánto tiempo invierten en llenar papelería?

FARMACIA:

22.5 ¿Cómo es el mecanismo (proceso) de distribución para recibir ácido fólico-hierro en la unidad? Y calcio?

22.6 ¿Cómo se calcula necesidad?

22.7 ¿Siempre tienen suficiente? Ácido fólico-hierro? ¿Calcio?

PROMOTOR DE SALUD

22.9 ¿Las mujeres embarazadas, en general, aceptan vacunación?

22.10 ¿Qué aspectos hacen su trabajo más difícil?

22.11 ¿Qué podría hacer su trabajo más fácil en relación a vacunación de embarazadas? (problemas técnicos del procedimiento,…. ¿algo que se les dificulta?)

22.12 ¿Cuándo se cometen errores a que se deben, y que podría haber ayudado a evitarlos?

MEDICO

22.13 ¿A quién le toca revisar el esquema de vacunación de la embarazada (médico o enfermera)? Quien realmente lo hace siempre?

22.14 ¿Se entregan mosquiteros e insecticida (DEET) rutinariamente a embarazadas?

22.15 ¿En su experiencia, las embarazadas le han comentado si tienen algún problema para tomar el ácido fólico con hierro? En caso afirmativo, ¿De todas formas se toman el medicamento?

22.16 ¿Cuánto tiempo invierten en llenar papelería?

23. PAPELERÍA QUE SE UTILIZA EN UN EXPEDIENTE INSCRIPCIÓN PRENATAL

1) Hoja filtro para identificación de factores de riesgo
2) HCPB (historia clínica prenatal básica) (conocida como “CLAP”) con todos los datos de atención prenatal: para la mujer embarazada

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3) HCPB con todos los datos de atención prenatal: para el expediente
4) Plan de parto
5) Historia clínica
6) Solicitud de batería de exámenes prenatales (2 o mas hojas):
   i. VIH por separado
   ii. Hemograma
   iii. tipo de sangre
   iv. glucosa,
   v. examen de orina
   vi. examen de Sífilis,
   vii. coproparasitoscópico en heces
7) Solicitud de citología (papanicolau)
8) Solicitud de Nugent (para descartar infección vaginal)
9) Recetas individuales para cada medicamento (mínimo es ácido fólico con hierro)
10) Solicitud de ultrasonido prenatal (USG)
11) Solicitud de citas: seguimiento prenatal, nutrición, psicología, odontología
12) Solicitud de referencia o de interconsulta a otro hospital de ser necesario
13) Otros: _____

III. Para la enfermera de vacunación:

24. ¿Cómo se monitorean las existencias de vacunas maternas en su establecimiento?	
25. ¿Cómo se calculan las proyecciones de vacunas maternas en su establecimiento?	
26. ¿Podría describir el almacenamiento de las vacunas maternas, tal como: capacidad (¿dosis y volumen en metros cúbicos, refrigeración, duración entre reabastecimiento?	
26.1 Capacidad instalada	
26.2 Cadena de frio	
26.3 Logística y duración entre reabastecimiento	
27. Por favor describa la frecuencia con que las vacunas son traídas a la instalación	1. ◯ Cada semana 2. ◯ Cada mes 3. ◯ Cada seis meses 4. ◯ Cada año 5. ◯ Otra
28. ¿Alguna vez ha habido un mal funcionamiento de la cámara de frío (o refrigerador) en los últimos 5 años en este establecimiento?	1. ◯ Si 2. ◯ No
29. ¿Cuantas veces o que tan seguido funciona mal?	
30. ¿Qué se hace en esas ocasiones para prevenir la perdida de cadena de frio?	

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31. ¿En esas ocasiones, hay alguna parte del lineamiento que es difícil cumplir o no siempre se sigue?	
32. ¿Cómo se planea y maneja el almacenamiento de las vacunas maternas durante la Semana de las Américas?	
33. Considerando todas las vacunas que se recibe normalmente durante el ano ¿cuántos termos tomaría para almacenar todas las vacunas en esta unidad?	
34. ¿Cuantos termos se tomaría para almacenar solo las vacunas maternas?	
35. ¿Cuántos termos se necesitan para almacenar todas las vacunas durante la Semana de las Américas?	
36. ¿Qué otros productos se almacenan en el refrigerador asignado para vacunas?	
37. ¿Mantiene un registro local de las mujeres embarazadas en su área de responsabilidad?	1. ◯ Si 2. ◯ No
38. Si es así, ¿se busca vacunar en casa a las mujeres embarazadas a las que les falte vacunar según el registro?	
39. ¿Puedo ver la vacuna que tiene en uso? (anotar si es multidosis / dosis única, fabricante, tomar foto del producto)	3. ◯ Es multidosis 4. ◯ Es dosis única Nombre del fabricante: _____
40. Permito tomar foto: --- caso afirmativo tomar foto	2. ◯ Si 2. ◯ No
41. ¿Dónde se almacenan los suministros ofrecidos durante la consulta prenatal que no necesitan refrigeración? (Por ejemplo, medicamentos o multivitamínicos, apoyo nutricional)	

IV. Barreras de acceso

42. ¿En su experiencia, qué porcentaje de mujeres embarazadas diría usted que está recibiendo las vacunas prenatales a tiempo?	Influenza: _____% Td: _____ Tdap: _____
En El Salvador, las vacunas maternas se administran como parte de la consulta prenatal. 43. ¿Cuáles son las ventajas de hacer esto?	
44. ¿Cuáles son las desventajas de hacer esto?	

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45.	¿Existe alguna situación en la que decide no ofrecer la vacuna a la embarazada?	
46. 47.	En su experiencia, ¿ha oído si otros compañeros médicos o enfermeras deciden no ofrecer la vacuna a embarazadas porque ellos mismos tienen ciertas percepciones negativas sobre la vacuna? Si es afirmativo, ¿son diferentes las percepciones negativas según el tipo de vacuna materna?	
48. 49.	¿Cuáles son algunas de las razones por las que una mujer podría no querer ser vacunada durante su embarazo? ¿Qué tan frecuente es esto?	
50.	Considerando el sistema de salud, la cultura, la situación económica, todo, ¿Qué contribuye a hacer más fácil que una mujer embarazada acuda a recibir las vacunas maternas?	
51.	Considerando el sistema de salud, la cultura, la situación económica, todo, ¿Qué contribuye a hacer más difícil que una mujer embarazada acuda a recibir las vacunas maternas? Sondear: costo, distancia, traslado, otras barreras.	

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V. Tecnologías para administración de vacunas

52. A continuación, le voy a mostrar unas fotos y voy a describir las diferentes tecnologías para administrar vacunas. Dígame lo que le gusta o no le gusta de estas				
Foto	**Descripción**	**Positivo**	**Negativo**	**Observación**
53. Por último, en base a lo que hemos hablado hoy y a sus experiencias personales y profesionales, ¿hay algo que le gustaría cambiar sobre las vacunas que aplican a las mujeres durante el embarazo?		1. ◯ Si 2. ◯ No		
54. ¿Qué cambios sugeriría?				
En la presentación:				
En su envasado:				
En la aplicación:				
En el almacenamiento:				
En la cadena de frio:				
En el transporte:				
En el descarte:				
55. ¿Otra sugerencia que usted considera haría su trabajo de vacunación más fácil o a la APN?				

Le informaré a la compañía que produce las vacunas sobre esta información tan importante

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Número de identific

Guía para la entrevista responsables de programa

Fecha: _____ Municipio: _____

UCSF: _____

Departamento: _____Zona: _____

VI. Perfil del responsable de programa

1. Puesto:	
2. Descripción de responsabilidades:	
3. Historial de trabajo antes de esta posición: 3.1 Número años en el puesto actual: ___	

VII. Atención Prenatal (APN). **Para los responsables de programa nacional PVI**

4. ¿Quién es responsable de adquirir los otros suministros de medicamentos para la atención materna? <Pregunta para la Directora>	1. ◯ Unidad de abastecimiento 2. ◯ Dirección de medicamentos y producto sanitarios 3. ◯ Otros: (Especificar):_____
5. ¿Cuáles son los requisitos de almacenamiento para medicamentos de atención prenatal y maternal? (ejemplo, oxitocina, sulfato de magnesio, etc.)	
Medicamentos sin control	requisitos de almacenamiento
carbetusina	
acetaminofén	
vitaminas	
nutrientes	
Medicamentos controlados	
MISOPROSTOL,	
oxítona,	
maleato de ergonovina	

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VIII. Obstáculos en la vacunación materna

Para todos los responsables de programa APN a nivel Nacional, Regional, SIBASI

Se nos ha informado que la cobertura de inscripción prenatal entre mujeres de 10 a 49 años, en los últimos 3 años oscila entre 76% y 88%....

Cobertura de inscripción prenatal de 10 a 49 años						
2009	2010	2011	2012	2013	2014	2015
83.20%	87.10%	90.70%	85.30%	76.60%	84%	88.10%

Además, que..
El Número de visitas para *Control prenatal básico* (mujeres sin riesgo o sin complicaciones) es **5 visitas** (incluye inscripción y subsecuente)

Número de visita para *Control prenatal especializado* (mujeres con morbilidad previa o complicaciones durante el embarazo) debe ser **cada 15 días**

6. ¿En su opinión, cuáles son los obstáculos para proveer la atención prenatal y alcanzar una mayor cobertura?

Nivel de atención	Obstáculos para el control prenatal dentro de un establecimiento de salud
Central	
Región	
SIBASI	
Hospital	
Establecimiento de salud	

7. ¿Cuáles considera usted son los obstáculos para buscar y recibir vacunación durante el embarazo?

NIvel de atención	Obstáculos para la vacunación materna dentro de un establecimiento de salud
Central	
Región	
SIBASI	

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Hospital	
Establecimiento de salud	

[En entrevista de responsables de APN, salta a la sección de productos combinados]

IX. Vacunación materna

Para los responsables de programa nacional de Programa de Vacunaciones e Inmunizaciones (PVI)

8. ¿Cuáles son las vacunas que ofrece el MINSAL para la mujer embarazada?	*Las vacunas que ofrece el MINSAL para la mujer embarazada son Td, Tdpa; y durante la campaña la Semana de las Américas se vacuna contra la influenza estacional combinad*
9. ¿De dónde se adquieren las vacunas maternas?	*Se adquieren a través del Fondo Rotatorio, siendo el responsable de la adquisición el MINSAL a través de Programa de Vacunaciones e Inmunizaciones (PVI)*
10. ¿Quién es responsable de la adquisición de vacunas maternas, el PVI o un programa separado?	*Programa de Vacunaciones e Inmunizaciones (PVI)*
11. ¿Cuál es el mecanismo de compra de vacunas maternas e insumos necesarios para su administración? (sondear: escala, compra directa, licitación)	*El mecanismo de compra de vacunas maternas, jeringas y cajas descartables para su administración es a gran escala, a través del Fondo Rotatorio, el resto de suministros como algodón, papelería se realiza compra nacional a través de licitación*
12. ¿Cómo se **MONITOREAN** las existencias de vacunas maternas e insumos?	*A través del sistema único e vacunación (dosis aplicadas) y del movimiento de biológicos*
13. ¿**Cómo se calculan las proyecciones** nacionales de **vacunas** maternas e insumos?	
14. ¿Cuál es el mecanismo para determinar si la **capacidad de la cadena de frío** necesita incrementarse? 14.1 ¿Cuándo fue la **última vez que se fortaleció la cadena de frío** a nivel nacional, regional, SIBASI, local?	
15. ¿Cómo participa el nivel regional, SIBASI y local en el cálculo de vacunas maternas e	

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insumos necesarios para su administración?	
16. ¿**Cómo participa el nivel regional**, SIBASI y local en el cálculo de las necesidades de cadena de frío?	
17. ¿Podría describir el almacenamiento de cadena de frío de las vacunas maternas a nivel central?	
18. Si las vacunas maternas NO se almacenan separadamente de las vacunas del PVI.. ¿En qué momento se separan las vacunas maternas para las visitas de atención prenatal (APN)?	

19. ¿Las vacunas se almacenan refrigeran con otros suministros?

	Si	**No**
Nivel nacional:	◯	◯
Nivel regional:	◯	◯
Nivel SIBASI:	◯	◯
Nivel local	◯	◯

20. ¿Alguna vez ha habido un mal funcionamiento del cuarto frío en su experiencia en los últimos 5 años a nivel nacional? 21. ¿Cuantas veces? ***<Preguntar a Director Regional, todos los niveles de PVI>***	1. ◯ Si 2. ◯ No
22. ¿Cuál es el lineamiento establecido cuando esto sucede?	
23. ¿**Qué lineamiento se le dificultado cumplir** cuando hay mal funcionamiento de la cuarto frio? ***<preguntar a PVI y Regional>***	

24. ¿Cómo se planea y maneja el almacenamiento de las vacunas maternas durante la Semana de las Américas? **--<preguntar a todos>**

Planificación:	

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Como se maneja el almacenamiento de vacunas maternas:	

25. ¿Podría describir el mecanismo de distribución de vacunas maternas e insumos desde el Centro Nacional de Biológico (CENABI) hasta el nivel local? (sondear: cada cuando, forma de transporte, obstáculos) -----**<preguntar a todos>**

Región	
SiBASI	
Establecimiento de salud	
Sector salud ISSS	
Sector salud Bienestar magisterial	
Sector salud Batallón de Sanidad Militar	
Sector salud proveedor privado	

26. ¿La Planificación o la distribución de las vacunas maternas está en relación a otro suministro que utilice cadena de frio? 27. ¿Explicar por qué? **<confirmar…>**	1. ◯ Si 2. ◯ No
28. ¿Las vacunas maternas están vinculadas a otras cadenas de suministro de productos (como el resto del PVI)? (u otros medicamentos almacenados en la cadena de frío) 29. Si la respuesta es Sí, ¿cuáles suministros?	1. ◯ Si 2. ◯ No

x. Nueva vacuna contra el Zika. **Para los responsables de PVI nacional**

30. ¿Cuáles son las consideraciones clave a la hora de decidir si introducir o no un nuevo medicamento o vacuna en un programa rutinario del MINSAL como son los servicios de APN?

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(Preguntar sobre costo, disponibilidad, capacidad de la cadena de frío, entrenamiento, otros factores).	
Política	
Carga de la enfermedad	
Seguridad, eficacia y accesibilidad de la vacuna	
Financiamiento	
Logística y programática de la cadena de frio	
Logística y programática de notificación	
ESAVI (Efectos Supuestamente Asociados a las Vacunación e Inmunización)	
Entrenamiento	
Opinión de organismos	
31. ¿Cuál es el proceso para introducir una nueva vacuna, específicamente ZIKA por el PVI MINSAL	
32. Quien aprobaría la vacuna	
33. Quien adquiriría la vacuna:	
34. ¿Qué cadena de suministro se utilizaría (PVI o APN, si es que está separado)?	
35. ¿Dónde se almacenaría?	
36. ¿Quién daría las vacunas Zika (los trabajadores de salud del PVI o de APN?)	◯ los trabajadores de salud del PVI ◯ los trabajadores de salud del APN
37. ¿SI la vacuna estuviera disponible que nivel aplicaría la vacuna y bajo qué estrategia de salud se indicaría?	

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38. ¿Habría campañas de para incrementar cobertura si / cuando se introduzca la vacunación contra Zika por primera vez?	1. ◯ Si 2. ◯ No
39. ¿Se han llevado a cabo estudios relacionados al Zika o a la vacuna contra Zika aquí en El Salvador?	1. ◯ Si 2. ◯ No
40. ¿Cuáles fueron los desafíos para la implementación de esos estudios?	
41. ¿Cuál sería el rol del programa de APN si se incluyera la vacuna Zika?	

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XI. Situación de la vacuna contra el dengue. **Para los responsables de programa nacional PVI**

Nos enteramos de que Sanofi llevó a cabo un estudio de la vacuna contra el Dengue en El Salvador	
42. ¿Cuál es el estado de ese estudio?	
43. ¿Existen otros estudios en curso o previstos?	1. ◯ Si 2. ◯ No
44. ¿Cuáles?:	
45. ¿Está el MINSAL considerando incluir esa vacuna en el esquema básico de inmunización?	1. ◯ Si 2. ◯ No
46. En caso afirmativo, ¿a qué población se destinaría?	
47. ¿Hay planes para realizar estudios de vacunación contra el dengue durante el embarazo? 47.1¿Cuáles?	1. ◯ Si 2. ◯ No
48. ¿Existen otras vacunas actualmente en discusión para su inclusión en el plan de inmunización?	1. ◯ Si 2. ◯ No
49. En caso afirmativo ¿Cuáles?	

XII. Introducción de nuevos productos combinados. **Para los responsables de programa nacional PVI y APN ----<Preguntar solamente a la Dra. Nora Villatoro>**

Existen varias definiciones de un producto combinado. En nuestro caso, estamos interesados en conocer más sobre el uso de productos combinados en el que un biológico o medicamento y un dispositivo de administración se ponen juntos al momento de la fabricación. Por ejemplo, los parches anticonceptivos combinan el anticonceptivo con el dispositivo de administración transdérmica en un solo producto. Una jeringa precargada también se considera un producto combinado porque el fabricante combina el medicamento y la jeringa en el punto de fabricación.	
50. ¿Cuáles son las consideraciones clave a la hora de decidir si se introduce o no un nuevo producto combinado en un programa rutinario como los servicios de APN y PVI?	
51. ¿Cuál es un ejemplo de un producto combinado que el MINSAL compró para su uso en el sector público?	

Fecha	Producto

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52. ¿Cómo fue el proceso para la toma de decisión de comenzar a utilizar ese producto combinado?	
53. ¿Cuánto tiempo se tardó el proceso, desde el momento que se decidió introducirla hasta aprobar el nuevo producto combinado *Sondear hasta el momento que ingresó al país por primera vez*	
54. ¿Qué estudios / datos se usaron para apoyar ese proceso de toma de decisiones?	
55. ¿Qué adaptaciones de la cadena de suministro fueron necesarias para acomodar el producto?	

I. Vacunación materna. **Para los responsables de programa regional y SIBASI ----<Preguntar a todos >**

56. ¿Cómo se monitorean las existencias de vacunas maternas e insumos necesarios para su administración?	
57. ¿Cómo se calculan las proyecciones de vacunas maternas e insumos?	
58. ¿Podría describir el almacenamiento de cadena de frío de vacunas maternas en su nivel de responsabilidad?	

59. ¿Qué tan grandes son los refrigeradores y qué tipo (fabricante)?

Tamaño de refrigeradores	Tipo (fabricante)

60. ¿Qué tan grandes son los cuartos fríos y refrigeradores y de qué tipo? Tamaño/volumen/Fabricante:

	tipo	Tamaño/volumen
Nivel regional:		
Nivel SIBASI:		
Nivel local		

Instalaciones de almacenamiento biológico/Niveles	Central	Regional	SIBASI	Hospital	Establecimiento de salud
Cuartos fríos					
Refrigeradoras verticales					
Refrigeradoras horizontales					
Cajas frías (Ken Sellers)					
Termos fríos					

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61. ¿Con qué frecuencia reciben nuevos suministros de vacunas maternas?	1. ◯ Diaria 2. ◯ semana 3. ◯ mensual 4. ◯ cada seis meses 5. ◯ cada año
62. ¿De dónde?	
63. Quien lo abastece	
64. ¿Las vacunas para la mujer embarazada se almacenan separadamente de las otras vacunas del Programa de Vacunaciones e Inmunizaciones (PVI)?	1. ◯ Si 2. ◯ No
65. S la respuesta es No ¿en qué momento se separan las vacunas maternas para las visitas de atención prenatal (APN)?	
66. ¿Se refrigeran con otros suministros?	1. ◯ Si 2. ◯ No
67. ¿Cada cuando sucede el reabastecimiento de vacunas maternas?	

Comparten con otros suministros Instalaciones de almacenamiento biológico/Niveles	Central	Regional	SIBASI	Hospital	Establecimiento de salud
Medicamentos					
Vacunas para animales					

68. ¿Alguna vez ha habido un mal funcionamiento de la cámara fría en su experiencia en los últimos 5 años, en su nivel de responsabilidad?	1. ◯ Si 2. ◯ No
69. ¿Cuantas veces?	
70. ¿Cuál es el lineamiento establecido cuando esto suceda?	
71. ¿Qué lineamiento se le dificultado cumplir cuando hay mal funcionamiento de la cuarto frio?	

72. ¿Cómo se planea y maneja el almacenamiento de las vacunas maternas durante la Semana de las Américas?

Planificación	Manejo del almacenamiento

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II. Obstáculos en la vacunación materna.

Para todos los responsables de programa nacional, regional, SIBASI, tanto del PVI y APN

Se nos ha informado que la cobertura de inscripción prenatal entre mujeres de 10 a 49 años, en los últimos 3 años oscila entre 76% y 88%....

Cobertura de inscripción prenatal de 10 a 49 años						
2009	2010	2011	2012	2013	2014	2015
83.20%	87.10%	90.70%	85.30%	76.60%	84%	88.10%

Además, que..
El Número de visitas para *Control prenatal básico* (mujeres sin riesgo o sin complicaciones) es **5 visitas** (incluye inscripción y subsecuente)

Número de visita para *Control prenatal especializado* (mujeres con morbilidad previa o complicaciones durante el embarazo) debe ser **cada 15 días**

73. ¿Cuáles considera usted son los obstáculos para proveer la atención prenatal y alcanzar una mayor cobertura?

Nivel de atención	Obstáculos para el control prenatal dentro de un establecimiento de salud
Central	
Región	
SIBASI	
Hospital	
Establecimiento de salud	

74. ¿Cuáles considera usted son los obstáculos para buscar y recibir vacunación durante el embarazo?

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Nivel de atención	Obstáculos para la vacunación materna dentro de un establecimiento de salud
Central	
Región	
SIBASI	
Hospital	
Establecimiento de salud	

PREGUNTAS PARA EL PROMOTOR DE SALUD

1. El bote de plástico improvisado que usan para tirar las agujas, tiene cloro adentro o está seco? En qué circunstancias le ponen cloro?
2. Preguntas al promotor de salud de cada unidad:
    a. Cuantas localidades visitan a la semana?
    b. Cuantas veces a la semana salen a vacunar?
    c. Cuantas dosis de vacuna, y cuantos (y cuales) frascos de vacuna llevan en el termo en un día promedio?
    d. Cuantas dosis de vacuna administran en un día promedio?
    e. Cuantas embarazadas ven en un día promedio?
    f. Como se transportan a las localidades de su responsabilidad?
    g. Cuanto tiempo toma llegar a las localidades?

h. Regresan siempre a su casa al final del día o hay ocasiones donde se quedan a dormir en la localidad que visitan?

i. Tienen alguna estación fija en la localidad para atender a la gente, o solo visitan de casa en casa?

j. Que podría ayudar a hacer su trabajo diario más fácil o mejor?

k. Cuáles son los retos más grandes que se enfrenta para poder vacunar a las embarazadas en las localidades?

l. Que piensan de las diferentes tecnologías innovadoras?

m. Cómo piensan que estas tecnologías les ayudarían a hacer más fácil las vacunación de embarazadas?

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Número de identific

GUÍA DE OBSERVACIÓN EN LA CLÍNICA

Fecha: _____ Municipio: _____

UCSF: _____

Departamento: _____Zona: _____

XIII. Ambiente

75. Temperatura del ambiente en el momento de la visita	
76. Humedad: *https://www.wunderground.com/*	◯ Alto ◯ Medio ◯ Bajo
77. Estructura del edificio	
3.1 Número de habitaciones en general:	
3.2 Número de consultorios para la atención prenatal:	
3.3 Número de consultorios para la vacunación materna:	
3.4 Material predominante del edificio:	1. ◯ Concreto 2. ◯ Madera 3. ◯ Otros:(especificar):_____
78. Estado general del edificio	1. ◯ Excelente 2. ◯ Bueno 3. ◯ Malo
79. ¿Existe un área de espera al aire Libre?	1. ◯ Si 2. ◯ No
80. Distancia del centro de suministro de vacunas del nivel responsable de abastecimiento más cercano (en kilómetros)	
81. Distancia (en kilómetros) de la unidad de salud a la carretera principal más cercana que conecte a otras poblaciones (para las unidades rurales que visitaremos):	

XIV. Perfil de la clínica

82. Nivel de atención:	◯ Primaria ◯ Secundaria ◯ Terciaria ◯ Privada ◯ Otro:_____

83. Servicios ofrecidos, todos los departamentos:

Servicios ofrecidos	Si	No
9.1 Área para atención de primer nivel de atención (bajo riesgo)	◯	◯
9.2 Emergencia medicina	◯	◯
9.3 Emergencia gineco obstetricia	◯	◯
9.4 Emergencia cirugía/ortopedia	◯	◯
9.5 Emergencia pediatría/neonatología	◯	◯
9.6 Máxima urgencia de niños	◯	◯

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9.7 Máxima urgencia de adultos	◯	◯	
9.8 Máxima pediatría	◯	◯	
9.9 Máxima ginecología	◯	◯	
9.10 Pequeña cirugía	◯	◯	
9.11 Sala de operaciones de emergencia	◯	◯	
9.12 Sala de operaciones electiva	◯	◯	
9.13 Sala de partos	◯	◯	
9.14 Sala de recuperación	◯	◯	
9.15 Atención de recién nacido	◯	◯	
9.16 Terapia respiratoria	◯	◯	
9.17 Vacunación	◯	◯	
9.18 Radiología	◯	◯	
9.19 USG (Ultrasonografía)	◯	◯	
9.20 Farmacia	◯	◯	
9.21 Laboratorio clínico	◯	◯	
9.22 Hospitalización	◯	◯	
9.23 Consulta externa	◯	◯	
9.24 Odontología	◯	◯	
9.25 Nutrición	◯	◯	
9.26 Psicología	◯	◯	
9.27 Otra:	◯	◯	
	◯	◯	

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XV. Observación de la clínica APN

84. ¿Número consultorios donde trabaja el entrevistado (medico, enfermera, la vacunadora, etc.)?		
85. Observar ¿Qué tareas realiza el entrevistado durante las horas de observación? 11.1 Anotar si se proporciona o no consejería para evitar picaduras por mosquitos. 11.2 Anotar si en consulta de inscripción el medico/enfermera que está dando consulta, si solicita USG, consultas a nutrición / odontología / psicología.		
86. Observar ¿Dónde pasa la mayor parte de su tiempo?--Describa los entornos / lugares donde se encuentra a lo largo de las horas de observación:		
87. Describa las superficies de trabajo, ¿qué hay en ellas?		
87.1 Mesa de trabajo		
87.2 Escritorio		
87.3 Silla de personal		

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87.4 Silla para usuaria		
87.5 Lámpara de ganso		
87.6 Mueble para material de atención		
87.7 Cama ginecológica (Canapé)		
87.8 Área para material de descarte		
87.9 Otro.		
88. Observar ¿# viajes entre habitaciones durante las actividades de rutina?		
89. ¿Qué hace el entrevistado en cada viaje,		
90. ¿Por qué necesita hacer cada viaje?		
91. Observar y describir las interacciones del entrevistado con cosas / herramientas de trabajo (aparatos, caja de seguridad, caja de residuos, guantes, etc.)		

92. Flujo típico del paciente: ¿por dónde empiezan, cuánto tiempo toman, ¿dónde terminan? ¿qué usan?

	Recursos que utilizan	Tiempo
92.1 Inicio		
92.2 Paso 2		

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92.3 Paso 3		
92.4 Paso 4		
92.5 Paso 5		
92.6 Paso final		
93. Observar y describir las situaciones en el flujo de trabajo que parecen provocar fricción o frustración.		
94. Otras observaciones:		

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SERVICIO DE VACUNACIÓN (preguntas para la enfermera vacunadora)

20.1 ¿En qué área o cuarto se ubica el refrigerador donde se almacena la vacuna?

20.2 Ese cuarto ¿Cuenta con aire acondicionado?

20.3 ¿Existen refrigeradores en otras áreas además de ese cuarto?

95. ¿Con qué frecuencia se producen apagones en esta unidad de salud?	1. ◯ Siempre 2. ◯ Casi siempre 3. ◯ Algunas veces 4. ◯ Muy rara vez 5. ◯ Nunca
96. ¿Hay un generador de electricidad de respaldo para la refrigeradora de vacunas?	1. ◯ Si 2. ◯ No
97. ¿Cuántos refrigeradores se están usando ahora mismo en esta área?	

98. (Si se está en una unidad de salud pequeña, contar todos los refrigeradores. Si se está en un hospital, contar los refrigeradores del área de vacunación y atención prenatal

99. Para cada refrigerador en uso, indicar:	Tamaño (medidas)	capacidad (número de vacunas que puede guardar)	volumen en metros cúbicos	Contenido actual en el refrigerador (tipo de vacunas, medicamentos):

100. ¿Considera usted que normalmente tiene suficiente espacio de refrigeración para almacenar vacunas y medicamentos?	
101. ¿Qué pasa con la capacidad instalada durante la semana de vacunación (Semana de las Américas), tiene que usar almacenamiento adicional?	◯ Si 2. ◯ No
102. ¿De qué tipo?	
103. ¿Cuantos termos tiene actualmente?	

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104. ¿Con qué frecuencia se arruina un refrigerador?	1. ◯ Siempre 2. ◯ Casi siempre 3. ◯ Algunas veces 4. ◯ Muy rara vez 5. ◯ Nunca
105. ¿En cuánto tiempo se repara el refrigerador arruinado?	1. ◯ 2 o 3 días 2. ◯ Una semana 3. ◯ Dos o tres semanas 4. ◯ Un mes 5. ◯ Dos o tres meses 6. ◯ 6 meses 7. ◯ Un año 8. ◯ Varios años
106. ¿Qué hace usted con las vacunas cuando está arruinado el refrigerador?	
107. ¿Con qué frecuencia recibe suministro de vacuna? (especifique la vacuna materna si se almacena por separado-	
108. ¿Posee una programación para el suministro de vacuna	1. ◯ Si 2. ◯ No
109. ¿Cuál es la periodicidad de esa programación de suministro?	1. ◯ Semanal 2. ◯ Quincenal 3. ◯ Mensual 4. ◯ Bimensual 5. ◯ Trimestral 6. ◯ Otra (especificar):
110. Cuales fortalezas ve en su área de trabajo para la atención de la mujer embarazada	
111. ¿Cuáles dificultades observa en su área de trabajo que al superarlas podría mejorar la atención a la mujer embarazada?	

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SERVICIO DE ATENCIÓN PRENATAL (preguntas para la enfermera para atención prenatal)

112. En un día entre lunes a viernes ¿Cuánto personal se encuentra laborando aquí en APN?	

113. ¿Qué función tienen?

Personal	Médico ginecólogo	Médico general	Enfermera graduada	Enfermera auxiliar	Personal de farmacia	Personal de vacunación
39.1 Atención de mujer embarazada APN						
39.2 Atención de mujer embarazada por enfermedad						
39.3 Signos vitales						
39.4 Despacho de medicamento						
39.5 Consejería APN						
39.6 Consejería vacuna						

114. ¿Cuántas mujeres se atienden de APN en un día lunes a viernes?	
115. ¿Y en un día con mucha demanda?	
116. ¿Y en un día con poca demanda?	
117. ¿Cuál es el estatus socioeconómico de la mayoría de los pacientes?	
118. Nivel educativo que observa frecuentemente en la mujer embarazada (en los últimos 6meses):	1. ◯ Sin estudio 2. ◯ Primero a sexto 3. ◯ Tercer ciclo 4. ◯ Bachillerato 5. ◯ Técnico 6. ◯ Universitario
119. ¿Qué porcentaje de la población que se atiende en esta unidad pueden leer una indicación escrita?	
120. ¿Cuáles fortalezas ve en su área de trabajo para la atención de la mujer embarazada?	

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121. ¿Cuáles dificultades observa en su área de trabajo que al superarlas podría mejorar la atención a la mujer embarazada?	

Phase III PPT: Improving access to maternal vaccines in low-resource settings with novel packaging and delivery technologies

Results of Objective 3: Optimal pairings of maternal vaccines with packaging/delivery technologies

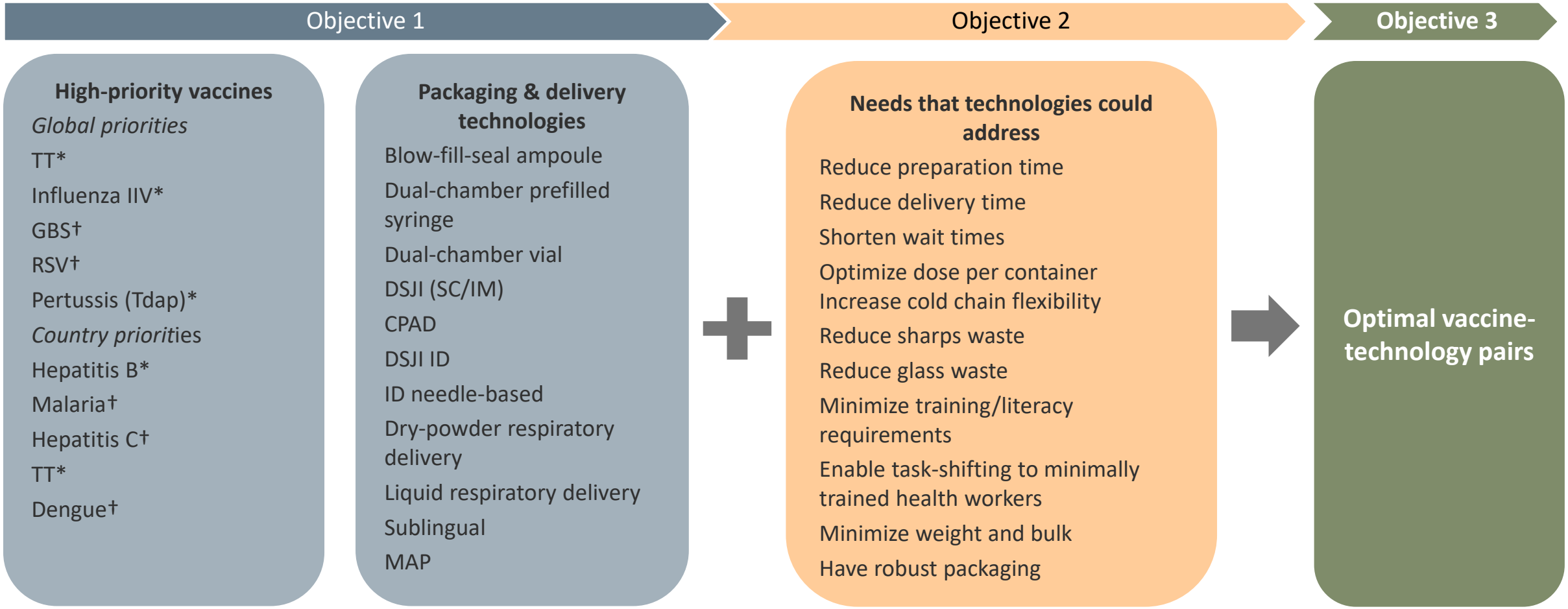
Devices and Tools

Vaccine and Pharmaceutical Delivery Technologies Team

November 30, 2017

PATH
A catalyst for global health

Background: Objectives 1 to 3



*Currently approved for use in pregnancy; †Investigational vaccines where presentations are not yet finalized.

Abbreviations: CPAD, compact, prefilled, autodisable device; DSJI, ; disposable-syringe jet injector; GBS, Group B *Streptococcus*; ID, intradermal; IIV, inactivated influenza vaccine; IM, intramuscular; MAP, microarray patch; RSV, respiratory syncytial virus; SC, subcutaneous; Tdap, tetanus, diphtheria, acellular pertussis; TT, tetanus toxoid.

Methods

Phase III Objective: Identify optimal pairings of high-priority vaccines and packaging/delivery technologies to address technical and programmatic feasibility requirements.

A. Identify high-priority vaccines and potential packaging/delivery technologies.
B. Eliminate nonviable vaccine-technology product pairs.
C. Prioritize pairs based on product attributes and identify pairs with the greatest potential net benefit to immunization delivery.
D. Map prioritized product pairs to the needs identified under Objective 2 and propose product pairs with the best potential to optimize introduction and uptake of maternal vaccines.

A. **Identify high-priority vaccines and potential packaging/delivery technologies.**

B. Eliminate nonviable vaccine-technology product pairs

C. Prioritize pairs based on product attributes and identify pairs with the greatest potential net benefit to immunization delivery.

D. Map prioritized product pairs to the needs identified under Objective 2 and propose product pairs with the best potential to optimize introduction and uptake of maternal vaccines.

Identify high-priority vaccines and technologies: Vaccines

High-Priority Vaccines	Current Vaccine Presentation
Global stakeholders (WHO, BMGF, FDA, NIH, PATH, Emory)	
TT*	Preserved liquid vaccine (thimerosal) in multidose vials
IIV*	Preserved liquid vaccine (thimerosal) in multidose vials
GBS†	Liquid vaccine in single-dose vial (no preservative)
RSV†	Liquid vaccine in single-dose vial (no preservative)
Tdap*	Preserved liquid vaccine (thimerosal) in multidose vials
Country stakeholders (Responses from 14 countries)	
Hepatitis B*	Preserved liquid vaccine (thimerosal) in multidose vials
Malaria†	Lyophilized vaccine in single-dose vial (no preservative)
Hepatitis C†	Liquid vaccine in single-dose vial (no preservative)
TT*	Preserved liquid vaccine (thimerosal) in multidose vials
Dengue†	Liquid vaccine in single-dose vial (no preservative)

*Currently approved for use in pregnancy; †Investigational vaccines where presentations are not yet finalized.

Abbreviations: GBS, Group B *Streptococcus*; IIV, inactivated influenza vaccine; RSV, respiratory syncytial virus; Tdap, tetanus, diphtheria, acellular pertussis ; TT, tetanus toxoid.

Identify high-priority vaccines and technologies: Technologies

Technology category	Technologies
Primary container technologies	Blow-fill-seal ampoule
	Dual-chamber vial—integrated reconstitution
IM/SC injection technologies (needle-free or prefilled)	Dual-chamber prefilled syringe—integrated reconstitution
	Disposable-syringe jet injectors—SC/IM delivery
	Compact, prefilled, autodisable device (CPAD)
ID injection technologies	Disposable-syringe jet injectors—ID delivery
	ID needle-based (e.g., mini-needle, hollow microneedles, needle hub adapters)
Respiratory formulation and delivery technologies	Dry-powder respiratory delivery
	Liquid respiratory delivery
Sublingual formulation and delivery technologies	Sublingual (e.g., fast-dissolving thin film, thermoresponsive gel, fast-dissolving tablet)
Other alternative routes of delivery	Microarray (microneedle) patches

Abbreviations: ID, intradermal; IM, intramuscular; SC, subcutaneous.

A. Identify high-priority vaccines and potential packaging/delivery technologies.

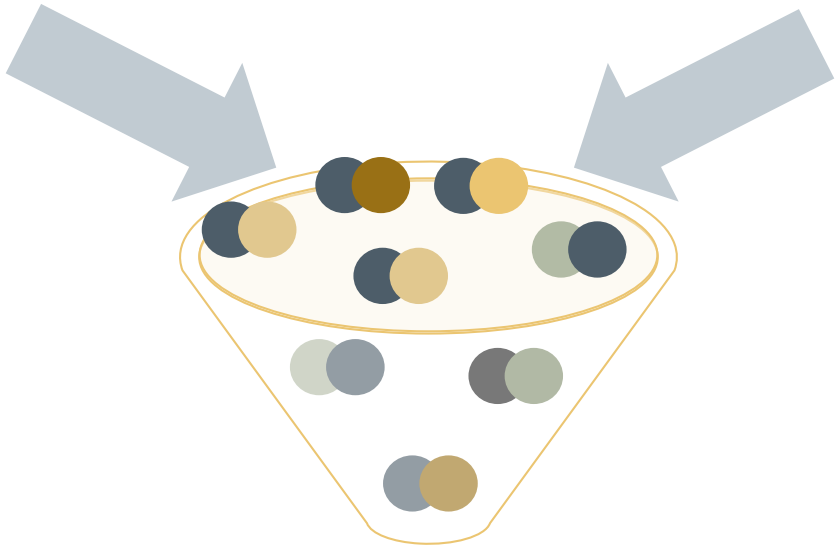
B. Eliminate nonviable vaccine-technology product pairs

C. Prioritize pairs based on product attributes and identify pairs with the greatest potential net benefit to immunization delivery.

D. Map prioritized product pairs to the needs identified under Objective 2 and propose product pairs with the best potential to optimize introduction and uptake of maternal vaccines.

Eliminate vaccine-technology pairs that are not technically feasible

High-Priority Vaccines
Global stakeholders
TT*
IIV*
GBS†
RSV†
Tdap*
Country stakeholders
Hepatitis B*
Malaria†
Hepatitis C†
TT*
Dengue†



1. Are the current vaccine formulation and context of use compatible with the vaccine technology?
2. Is reformulation a viable alternative?

Technologies
Blow-fill-seal ampoule
Dual-chamber vial—integrated reconstitution
Dual-chamber prefilled syringe—integrated reconstitution
Disposable-syringe jet injectors—SC/IM delivery
Compact, prefilled, autodisable device (CPAD)
Disposable-syringe jet injectors—ID delivery
ID needle-based (e.g., mini-needle, hollow microneedles, needle hub adapters)
Dry-powder respiratory delivery
Liquid respiratory delivery
Sublingual (e.g., fast-dissolving thin film, thermoresponsive gel, fast-dissolving tablet)
Microarray (microneedle) patches

Only viable pairings will go through the evaluation tool/process

Removal of pairs due to incompatibility of the technology with the vaccine formulation or context of use

*Currently approved for use in pregnancy; †Investigational vaccines where presentations are not yet finalized.

Abbreviations: GBS, Group B *Streptococcus*; IIV, inactivated influenza vaccine; RSV, respiratory syncytial virus; Tdap, tetanus, diphtheria, acellular pertussis ; TT, tetanus toxoid.

A. Identify high-priority vaccines and potential packaging/delivery technologies.

B. Eliminate nonviable vaccine-technology product pairs

C. Prioritize pairs based on product attributes and identify pairs with the greatest potential net benefit to immunization delivery.

D. Map prioritized product pairs to the needs identified under Objective 2 and propose product pairs with the best potential to optimize introduction and uptake of maternal vaccines.

Prioritize pairs based on product attributes: Scoring method

Vaccine-Technology Prioritization Tool

EFFICACY	EFFECTIVENESS	SAFETY	AVAILABILITY	COST	TECHNOLOGY READINESS	MANUFACTURING

Each vaccine technology receives a weighted score (-1, 0, 1) for each criterion; each criterion includes guidance to evaluate and determine a score:

- -1: suboptimal; significant issues, challenges, or drawbacks exist relative to current state.
- 0: neutral relative to current presentation.
- 1: improves upon current state in significant ways.

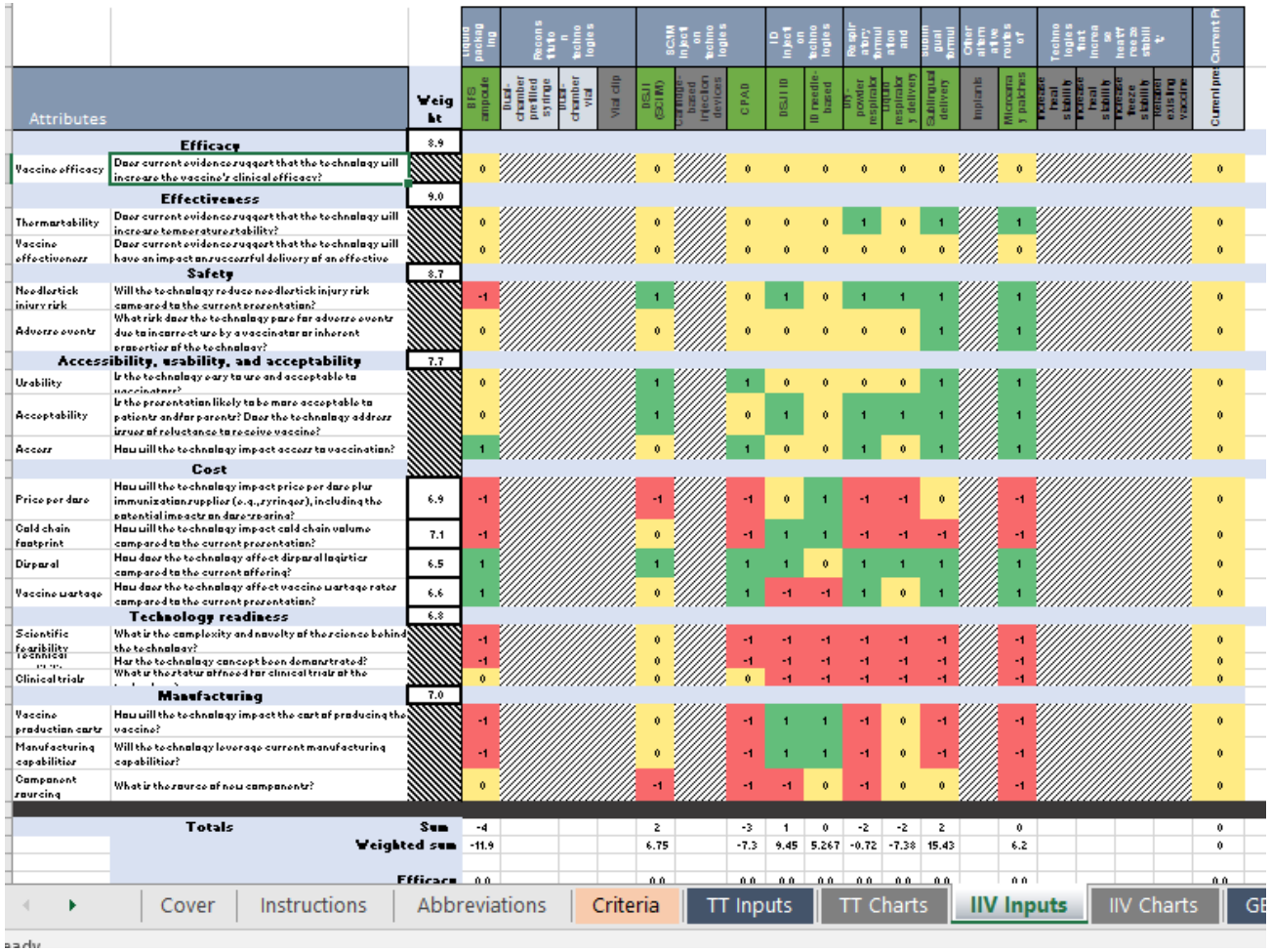
Scoring Criteria

Attributes	Evaluation basis	Scoring				
		-2	-1	0	1	2
Efficacy		***Optional score category, if more detailed comparative information is available.***				***Optional score category, if more detailed comparative information is available.***
Vaccine efficacy	Does current evidence suggest that the technology will increase the vaccine's clinical efficacy?	*Technology may significantly decrease vaccine efficacy*	Technology may decrease vaccine efficacy	Technology will not affect vaccine efficacy	Technology could increase vaccine efficacy	*Technology could significantly increase vaccine efficacy*
Effectiveness						
Thermostability	Does current evidence suggest that the technology will increase temperature stability?	*Current evidence suggests significantly decreased temperature stability*	Current evidence suggests decreased temperature stability	Current evidence suggests neither increase nor decrease in temperature stability, or no current evidence exists	Yes. Current evidence suggests there is potential to increase temperature stability (e.g., moving from VVM 2 to VVM 7)	*Yes. Current evidence suggests there is potential to significantly increase temperature stability (e.g., moving from VVM 2 to CTC)*
Vaccine effectiveness	Does current evidence suggest that the technology will have an impact on successful delivery of an effective dose?	*Significant negative impact on vaccine effectiveness*	Negative impact on vaccine effectiveness	Neutral impact (or no data) on vaccine effectiveness	Positive impact on vaccine effectiveness	*Very positive impact on vaccine effectiveness*
Safety						
Needlestick injury risk	Will the technology reduce needlestick injury risk compared to the current presentation?	*Significantly increases risk of needlestick injury*	Increases risk of needlestick injury	Same risk as current presentation	Reduces risk (e.g., needle-free, passive or active mechanism in place, reduces needle size)	*Significantly reduces risk (e.g., needle-free, passive or active mechanism in place, reduces needle size)*
Adverse events	What risk does the technology pose for adverse events due to incorrect use by a vaccinator or inherent properties of the technology?	*Significantly increases risk (e.g., introduces risk of bloodborne pathogen infection, sepsis, incorrect reconstitution risk)*	Increases risk (e.g., introduces risk of bloodborne pathogen infection, sepsis, incorrect reconstitution risk)	No impact on current adverse event risk	Reduces risk	*Significantly reduces risk*
Availability						
Usability	Is the technology easy to use and acceptable to vaccinators?	*Requires significantly greater skill or additional steps/more preparation time*	Requires greater skill or additional steps/more preparation time	No impact on skill, steps required, or preparation time	Requires less skill or reduces steps/less preparation time	*Requires significantly less skill or significantly reduces steps/preparation time*
Acceptability	Is the presentation likely to be more acceptable to patients and/or parents? Does the technology address issues of reluctance to receive vaccine?	*Significantly less acceptable*	Less acceptable	No impact on acceptability	Potential to increase acceptability	*Potential to significantly increase acceptability*
Accessibility	How will the technology impact access to vaccination?	*Potential to significantly decrease access (e.g., due to new presentation challenges)*	Potential to decrease access (e.g., due to new presentation challenges)	No impact on access	Potential to increase access (e.g.: due to improved presentation enabling alternative outreach settings)	*Potential to significantly increase access (e.g., due to improved presentation enabling alternative outreach settings)*

Scoring Criteria Continued

Attributes	Evaluation basis	Scoring				
		-2	-1	0	1	2
Efficacy		***Optional score category, if more detailed comparative information is available.***				***Optional score category, if more detailed comparative information is available.***
Cost						
COGs per dose	How will the technology impact COGs per dose plus immunization supplies (e.g., syringes), including the potential impact on dose-sparing?	*Significantly increases price/dose compared to current offering (e.g., immunization supplies cost increase)*	Increases price/dose compared to current offering (e.g., immunization supplies cost increase)	Does not increase price/dose compared to current offering	Reduces price/dose compared to current offering	*Significantly reduces price/dose compared to current offering*
Cold chain footprint	How will the technology impact cold chain volume compared to the current presentation?	*Significantly increases cold chain footprint*	Increases cold chain footprint	Maintains current cold chain footprint	Reduces cold chain footprint	*Significantly reduces cold chain footprint*
Disposal	How does the technology affect disposal logistics compared to the current offering?	*Significantly increases disposal logistics (e.g., introduces sharps)*	Increases disposal logistics (e.g., introduces sharps)	No impact on disposal logistics	Decreases disposal logistics (e.g., minimizes sharps)	*Significantly decreases disposal logistics (e.g., gets rid of sharps)*
Vaccine wastage	How does the technology affect vaccine wastage rates compared to the current presentation?	*Significantly increases wastage rate*	Increases wastage rate	Maintains wastage rate	Reduces wastage rate	*Significantly reduces wastage rate*
Technology readiness						
Scientific feasibility	What is the complexity and novelty of the science behind the technology?	*Technology + vaccine pairing represents novel technology development, and POC not established anywhere*	Some new scientific technology; POC conceivable.	Use of well-understood scientific principles and concepts		
Technical credibility	Has the technology concept been demonstrated?	*No previous technical experience or examples that demonstrate credibility of model*	Limited technical experience or examples demonstrating technical concept	High level of confidence—product already on the market.		
Clinical trials	What is the status/need for clinical trials of the technology?	*Clinical studies required; 5–10+ years development time.*	Clinical studies required	Clinical studies completed or not required		
Manufacturing						
Vaccine production costs	How will the technology impact the cost of producing the vaccine?	*Significantly increases production cost*	Increases production cost	Similar production costs	Reduces production cost	*Significantly reduces production cost*
Manufacturing capabilities	Will the technology leverage current manufacturing capabilities?	*Very disruptive; new manufacturing facilities, equipment, and processes needed*	Disruptive; new manufacturing facilities, equipment, and processes needed	Adaptation of existing manufacturing capabilities.	Capabilities partially align with manufacturing technology strategy, drive synergies, and reduce redundancies	*Capabilities fully align with manufacturing technology strategy, drive synergies, and reduce redundancies*
Component sourcing	What is the source of new components?	*Patent protected and single source*	Patent protected and single source	Similar flexibility in supplier options as components it is replacing	Increases supplier options	*Significantly increases supplier options*

Prioritize pairs based on product attributes: Scoring tool example (see Phase III Prioritization Matrix for complete results)



Abbreviations: BFS, blow-fill-seal; CPAD, compact, prefilled, autodisable device; DSJI, ; disposable-syringe jet injector; ID, intradermal; IM, intramuscular; SC, subcutaneous.

Prioritize pairs based on product attributes: Results of product pair scoring

		BFS ampoule	Dual-chamber prefilled syringe	Dual-chamber vial	DSJI (SC/IM)	CPAD	DSJI ID	ID needle-based	Dry-powder respiratory delivery	Liquid respiratory delivery	Sublingual delivery	Microarray patches
Weighted scores	TT	-11.9			-4.4	-2.8					8.5	6.2
	IIV	-11.9			6.8	-7.3	9.5	5.3	-0.7	-7.4	15.4	6.2
	GBS	4.5			-4.4	0.1	5.1	0.9	8.7	4.1	23.0	13.8
	RSV	4.5			-4.4	0.1	5.1	0.9	11.2	4.1	23.0	18.3
	Tdap	-14.2			-4.4	-5.0					8.5	6.2
	HepB	-11.9			-4.4	-2.8	-4.0	3.2	-3.0	6.6	8.5	6.2
	Malaria		-18.3	-11.5	0.0		5.1	0.9	6.7	6.6		9.3
	HepC	4.5			-4.4	-6.8	9.5	5.3	11.2	6.6		13.8
	Dengue	4.5			-4.4	-4.5	5.1	0.9				13.8

Gray: Eliminated—not technically feasible

Black: Negative value—may have a net negative impact compared to existing delivery format

Yellow: 0–10—may offer some benefit over existing delivery format

Green: > 10—may offer significant benefit over existing delivery format

Abbreviations: BFS, blow-fill-seal; CPAD, compact, prefilled, autodisable device; DSJI, ; disposable-syringe jet injector; GBS, Group B *Streptococcus*; HepB, hepatitis B; HepC, hepatitis C; ID, intradermal; IIV, inactivated influenza vaccine; IM, intramuscular; NA, not applicable; RSV, respiratory syncytial virus; SC, subcutaneous; Tdap, tetanus, diphtheria, acellular pertussis ; TT, tetanus toxoid.

Prioritize pairs based on product attributes: Product pairs for consideration

Vaccine	Optimal pairs (significant value over existing format)	Secondary pairs (some value over existing format)
TT	None	Sublingual delivery/MAPs
IIV	Sublingual delivery	ID needle-based/MAPs/DSJI (SC/IM/ID)
GBS	Sublingual delivery/MAPs	BFS ampoule/CPAD/DSJI ID/dry-powder respiratory delivery/liquid respiratory delivery/MAPs
RSV	Dry-powder respiratory delivery/sublingual delivery/MAPs	CPAD/ID needle-based/liquid respiratory delivery/BFS ampoule
Tdap	None	Sublingual delivery/MAPs
HepB	None	ID needle-based/MAPs/liquid respiratory delivery/sublingual delivery
Malaria	None	ID needle-based/DSJI (SC/IM)/liquid respiratory delivery/dry-powder respiratory delivery/MAPs
HepC	Dry-powder respiratory delivery / MAPs	BFS ampoule/ID needle-based/liquid respiratory delivery/DSJI ID
Dengue	MAPs	ID needle-based/BFS ampoule/DSJI ID

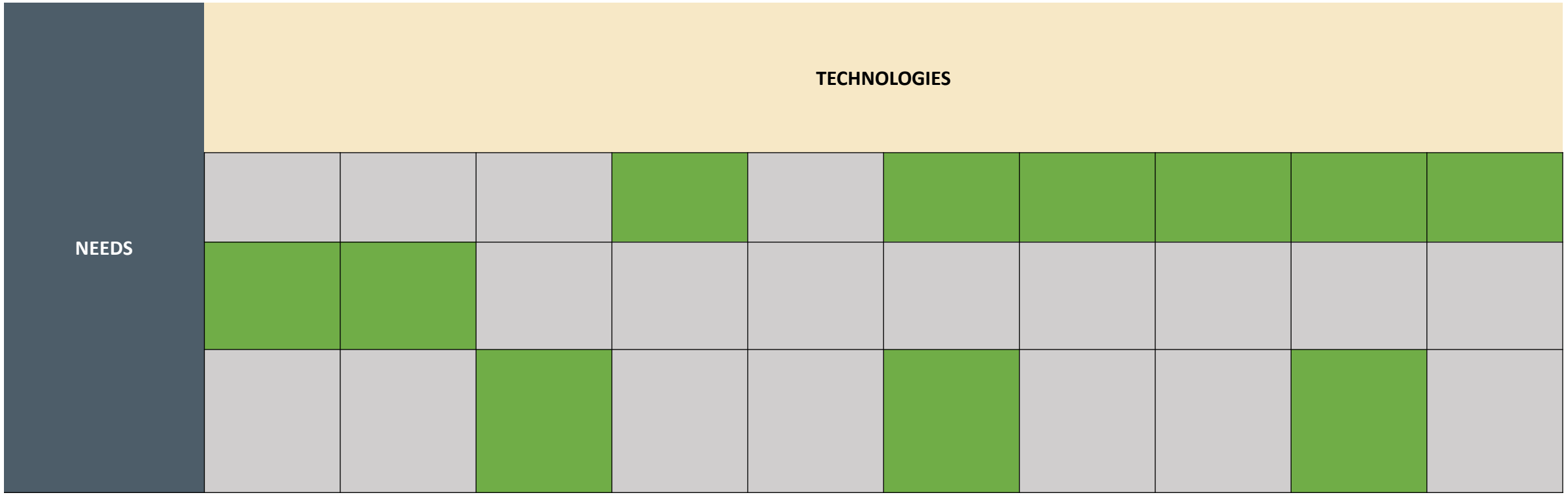
Abbreviations: BFS, blow-fill-seal; CPAD, compact, prefilled, autodisable device; DSJI, disposable-syringe jet injector; GBS, Group B *Streptococcus*; HepB, hepatitis B; HepC, hepatitis C; ID, intradermal; IIV, inactivated influenza vaccine; IM, intramuscular; MAP, microarray patch; RSV, respiratory syncytial virus; SC, subcutaneous; Tdap, tetanus, diphtheria, acellular pertussis ; TT, tetanus toxoid.

A. Identify high-priority vaccines and potential packaging/delivery technologies.
B. Eliminate nonviable vaccine-technology product pairs
C. Prioritize pairs based on product attributes and identify pairs with the greatest potential net benefit to immunization delivery.
D. **Map prioritized product pairs to the needs identified under Objective 2 and propose product pairs with the best potential to optimize introduction and uptake of maternal vaccines.**

Map technologies to needs: Results of needs assessment (Objective 2)

Constraint	Description	To address constraints, health care workers need a packaging/delivery technology that can:
Patient load.	Excessive patient volumes. Long wait times can result in loss to follow-up. Improvised time-saving measures, like prefilling syringes (which is against policy). Dose-tracking and dose-scheduling challenges.	Reduces preparation time (the time it takes to prepare the vaccine prior to administration). Reduces delivery time (the time it takes to administer the vaccine, once it is prepared for delivery). Enables task shifting to minimally trained vaccinators. Optimizes dose per container: Enables EPI stakeholders to rightsize the doses per container according to the target environment of use.
Limited cold chain.	Use of vaccine carriers to store daily supplies can result in accidental temperature excursions. Insufficient thermometers or other temperature indicators to ensure appropriate temperature conditions. Transportation challenges can exacerbate cold chain limitations. Vaccine vial monitors are not used consistently on all vials and are not consistently checked.	Increases thermostability to enhance cold chain flexibility and prevent vaccine damage during temperature excursions.
Limited sharps disposal.	Usable sharps containers are not consistently available in antenatal care rooms to properly dispose of sharps waste. Community health workers who provide home-based care must give injections while juggling all their supplies, which can increase needlestick injury risk.	Reduces sharps waste. Minimizes weight and bulk of supplies that community health workers need to transport to villages.
Variable training.	High staff turnover and/or duty rotation results in varying levels of training and missed opportunities for refresher training.	Minimizes training/literacy requirements. Enables task shifting to minimally trained vaccinators.
Access limitations.	Community health workers have to carry heavy vaccine carriers and supplies with them to the community via public transportation to administer vaccines.	Optimizes dose per container: Enables EPI stakeholders to rightsize the doses per container according to the target environment of use. Reduces glass waste. Minimizes weight and bulk of supplies that community health workers need to transport to villages. Ensures robust packaging to prevent damaged/broken supplies.

Technology impact on constraints



Abbreviations: GBS, Group B *Streptococcus*; HepB, hepatitis B; HepC, hepatitis C; IIV, inactivated influenza vaccine; RSV, respiratory syncytial virus; Tdap, tetanus, diphtheria, acellular pertussis; TT, tetanus toxoid; VVM, vaccine vial monitor.

Technology impact on constraints

	DSJI ID		Dry-powder respiratory delivery			Sublingual delivery		Microarray patches		
	Dengue, RSV	Malaria	IIV, Hep B	Malaria	RSV, HepC	IIV, HepB	GBS, RSV	Malaria, Hep C	HepB	GBS, RSV, HepC, Dengue
Standard delivery method	*Liquid vaccine in single-dose vial (no preservative)*	*Lyophilized vaccine in single-dose vial (no preservative)*	*Liquid vaccine with preservative in multidose vials*	*Lyophilized vaccine in single-dose vial (no preservative)*	*Liquid vaccine in single-dose vial (no preservative)*	*Preserved liquid vaccine (thimerosal) in multidose vials*	*Liquid vaccine in single-dose vial (no preservative)*	*Lyophilized vaccine in single-dose vial (no preservative)*	*Preserved liquid vaccine (thimerosal) in multidose vials*	*Liquid vaccine in single-dose vial (no preservative)*
Reduces preparation time (the time it takes to prepare the vaccine prior to administration)										
Reduces delivery time (the time it takes to administer the vaccine, once it is prepared for delivery)										
Optimizes dose per container: Enables EPI stakeholders to rightsize the doses per container according to the target environment of use										

Abbreviations: GBS, Group B *Streptococcus*; HepB, hepatitis B; HepC, hepatitis C; IIV, inactivated influenza vaccine; RSV, respiratory syncytial virus; Tdap, tetanus, diphtheria, acellular pertussis; TT, tetanus toxoid; VVM, vaccine vial monitor.

Scientific feasibility of global priority vaccines

Vaccine	Natural route of infection	Indication	Benefits to mother and child
Global priority vaccines			
TT*	*C. tetani* spores enter the body through contaminated wounds or tissue injury.	Birth-associated tetanus can cause severe disease. Mothers and infants can be infected through unhygienic delivery, poor postnatal practices, and cord care practices.	Protects mother and infant.
IIV*	Respiratory disease, transmitted mainly by droplets and aerosols.	Influenza causes more severe disease during pregnancy and may be harmful to the developing fetus.	Protects mother and infant.
GBS	GBS is a common bacteria that is often carried in the intestines, vagina, rectum, bladder or throat; mother to child transmission during vaginal delivery.	Although GBS is harmless in healthy adults, it can cause severe disease in infants infected at birth.	Protects mother and infant.
RSV	Respiratory transmission, droplets.	RSV can cause severe disease in infants. Children are at greatest risk when they are too young to be vaccinated. Maternal vaccination is considered the best strategy to protect young infants during the period of greatest vulnerability.	Protects infant.
Tdap*	Airborne, respiratory droplets; toxin mediated, bacteria attach to cilia of the respiratory epithelial cells.	Pertussis can cause severe disease in infants too young to be vaccinated. One strategy to protect the infant is to vaccinate the mother so she cannot transmit the disease to the infant. This strategy is called cocooning.	Protects infant; prevents mother from being a carrier to infect infant.

Scientific feasibility of country priority vaccines

Vaccine	Natural route of infection	Indication	Benefits to mother and child
Country priority vaccines			
HepB*	Transmitted by exposure of mucosal membranes or nonintact skin to infected blood or other specific bodily fluids; mother to child transmission.	HepB can cause disease in adults. Infants infected at birth are more likely to develop chronic HepB, which can cause serious health problems.	Protects mother and infant.
Malaria	Vector-borne disease.	Pregnant women are at increased risk of developing severe disease during pregnancy and malaria infection during pregnancy can lead to miscarriage, premature delivery, low birth weight, congenital infection, and/or perinatal death.	Protects mother and infant.
HepC	Infection typically spreads when blood contaminated with virus enters the bloodstream; although rare mother to child transmission is possible.	Although the disease is treatable, there is a link between HepC infection and slightly increased risk of intrauterine growth restriction and low birth weight in infants infected at birth.	Protects mother and infant.
TT*	*C. tetani* spores enter the body through contaminated wounds or tissue injury.	Birth-associated tetanus can cause severe disease. Mothers and infants can be infected through unhygienic delivery, poor postnatal practices, and cord care practices.	Protects mother and infant.
Dengue	Vector-borne disease.	Dengue can cause severe disease in pregnancy and be harmful to the developing fetus.	Protects mother and infant.

Optimal product pair 1: IIV + sublingual delivery

Technology overview

- The sublingual route (i.e., via the mucosal surfaces under the tongue) is an attractive option for vaccine and drug delivery because it is easy to administer and induces both systemic and mucosal immunity.
- Examples:
  - Thermoresponsive gel.
  - Fast-dissolving tablet.

Photo: PATH

Photo: PATH

Feasibility summary

- Technical feasibility: In animal studies, mice that were given hemagglutinin conjugated to transferrin via sublingual delivery induced a significant antibody and T cell response in both naïve animals and previously immunized animals. The immune response was able to protect virus against viral challenge.*
- Programmatic feasibility: Sublingual delivery can reduce preparation time, shorten wait times, optimize doses per container, increase cold chain flexibility, reduce sharps waste, reduce glass waste, minimize training/literacy requirements, enable task-shifting to minimally trained health workers, minimize weight and bulk, and have robust packaging.

*Mann JF, Tregoning JS, Aldon Y, Shattock RJ, McKay PF. CD71 targeting boosts immunogenicity of sublingually delivered influenza haemagglutinin antigen and protects against viral challenge in mice. Journal of Controlled Release. 2016;232:75–82.

Current presentation: preserved liquid vaccine (thiomerosal) in multidose vials.

Abbreviations: IIV, inactivated influenza vaccine.

Optimal product pair 2: GBS + sublingual delivery

Technology overview

- The sublingual route (i.e., via the mucosal surfaces under the tongue) is an attractive option for vaccine and drug delivery because it is easy to administer and induces both systemic and mucosal immunity.
- Examples:
  - Thermoresponsive gel.
  - Fast-dissolving tablet.

Photo: PATH

Photo: PATH

Feasibility summary

- Technical feasibility: In animal studies, mice that were immunized with GBS type III capsular polysaccharide-cholera toxin B subunit conjugate vaccine administered via peroral administration elicited high anti-CPS IgA and IgG antibody levels in the intestinal site.*
- Programmatic feasibility: Sublingual delivery can reduce preparation time, shorten wait times, optimize doses per container, increase cold chain flexibility, reduce sharps waste, reduce glass waste, minimize training/literacy requirements, enable task-shifting to minimally trained health workers, minimize weight and bulk, and have robust packaging.

*Shen X, Lagergård T, Yang Y, Lindblad M, Fredriksson M, Holmgren J. Systemic and mucosal immune responses in mice after mucosal immunization with group B streptococcus type III capsular polysaccharide-cholera toxin B subunit conjugate vaccine. Infection and Immunity. 2000;68(10):5749–5755.

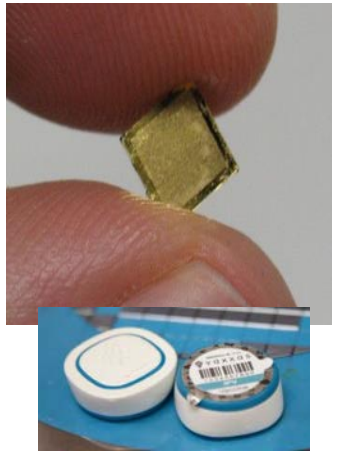
Current presentation: Assumed to be liquid vaccine in single-dose vial (no preservative).

Abbreviations: CPS, capsular polysaccharide; GBS, Group B *Streptococcus*; IgA, immunoglobulin A; IgG, immunoglobulin G; MAP, microarray patch.

Optimal product pair 3: GBS + MAP

Technology overview

- Patches consist of hundreds of tiny projections that deliver solid vaccine into the skin. Some platforms require an applicator for delivery (integrated or separate).
- Potential for enhanced thermostability (controlled temperature chain use) and controlled-release delivery (schedule reduction).



Photos: Vaxxas

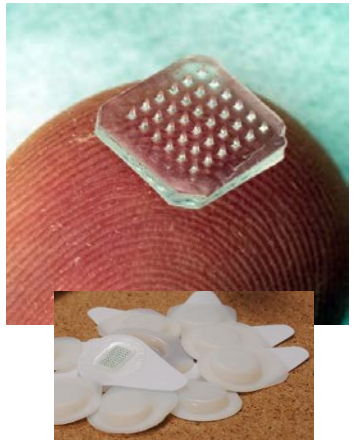


Photo: Georgia Tech

Feasibility summary

- Technical feasibility: Although a GBS MAP is possible based on the pathogen and natural route of infection, research on GBS MAPs has not been published.
- Programmatic feasibility: MAP delivery can reduce preparation time, shorten wait times, optimize doses per container, increase cold chain flexibility, reduce sharps waste, reduce glass waste, minimize training/literacy requirements, enable task-shifting to minimally trained health workers, minimize weight and bulk, and have robust packaging.

Current presentation: Assumed to be liquid vaccine in single-dose vial (no preservative)

Abbreviations: CTC, controlled temperature chain; GBS, Group B *Streptococcus*; MAP, microarray patch.

Optimal product pair 4: RSV + dry-powder respiratory delivery

Technology overview

- Dry-powder respiratory delivery technologies are needle-free, improve thermostability, deliver vaccine directly to the mucosa, and induce both systemic and mucosal immunity.
- Particularly useful for RSV because vaccine is delivered directly to mucosal surfaces in the respiratory tract.

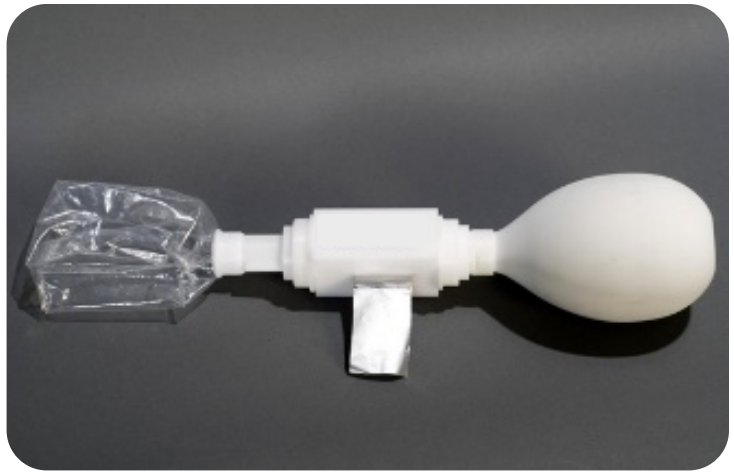


Photo: AKTIV-DRY

Feasibility summary

- Technical feasibility: Although dry-powder respiratory delivery has not been tested for RSV vaccine, a liquid respiratory RSV vaccine is currently being tested in a phase I clinical trial in adults.*
- A lyophilized RSV vaccine has also been tested in mice, which demonstrates the potential to reformulate a liquid RSV vaccine into a dry format.†
- Programmatic feasibility: Dry-powder respiratory delivery can shorten wait times, optimize doses per container, increase cold chain flexibility, reduce sharps waste, reduce glass waste, enable task-shifting to minimally trained health workers, and have robust packaging.

*Chris Chiu. Phase I Study for SynGEM, an Intranasal Respiratory Syncytial Virus (RSV) Prefusion F Subunit Candidate Vaccine (SynGEM). Available at: https://clinicaltrials.gov/ct2/show/NCT02958540.

†Levine S, Dillman TR, Montgomery PC. The envelope proteins from purified respiratory syncytial virus protect mice from intranasal virus challenge. Proceedings of the Society for Experimental Biology and Medicine. 1989 Apr;190(4):349–356.

Current presentation: Assumed to be liquid vaccine in single-dose vial (no preservative)

Abbreviations: IgA, immunoglobulin A; IgG, immunoglobulin G; RSV, respiratory syncytial virus.

Optimal product pair 5: RSV + sublingual delivery

Technology overview

- The sublingual route (i.e., via the mucosal surfaces under the tongue) is an attractive option for vaccine and drug delivery because it is easy to administer and induces both systemic and mucosal immunity.
- Examples:
  - Thermoresponsive gel.
  - Fast-dissolving tablet.

Photo: PATH

Photo: PATH

Feasibility summary

- Technical feasibility: In animal studies, mice that were immunized with a recombinant fusion protein RSV vaccine with a cholera toxin mucosal adjuvant elicited high serum IgG and mucosal IgA antibodies. This sublingual vaccine provided protection against both A and B subtypes of RSV.*
- Programmatic feasibility: Sublingual delivery can reduce preparation time, shorten wait times, optimize doses per container, increase cold chain flexibility, reduce sharps waste, reduce glass waste, minimize training/literacy requirements, enable task-shifting to minimally trained health workers, minimize weight and bulk, and have robust packaging.

* Lee JY, Chang J. Universal vaccine against respiratory syncytial virus A and B subtypes. PLoS One. 2017 Apr 6;12(4):e0175384. doi: 10.1371/journal.pone.0175384.

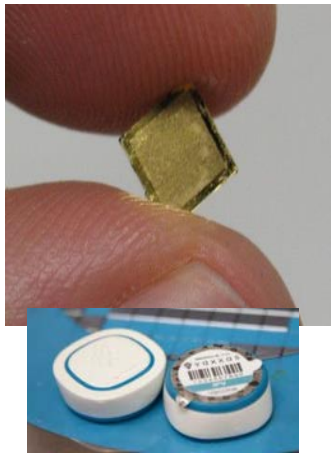
Current presentation: Assumed to be liquid vaccine in single-dose vial (no preservative)

Abbreviations: IgA, immunoglobulin A; IgG, immunoglobulin G; RSV, respiratory syncytial virus.

Optimal product pair 6: RSV + MAP

Technology overview

- Patches consist of hundreds of tiny projections that deliver solid vaccine into the skin. Some platforms require an applicator for delivery (integrated or separate).
- Potential for enhanced thermostability (controlled temperature chain use) and controlled-release delivery (schedule reduction).



Photos: Vaxxas

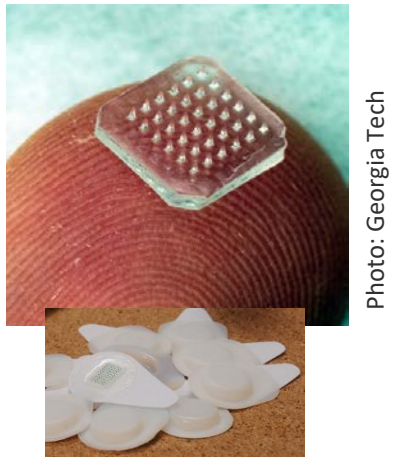


Photo: Georgia Tech

Feasibility summary

- Technical feasibility: MAP delivery of an RSV vaccine has not yet been demonstrated in preclinical studies in animals or clinical trials in humans.
- Programmatic feasibility: MAP delivery can reduce preparation time, shorten wait times, optimize doses per container, increase cold chain flexibility, reduce sharps waste, reduce glass waste, minimize training/literacy requirements, enable task-shifting to minimally trained health workers, minimize weight and bulk, and have robust packaging.

Current presentation: Assumed to be liquid vaccine in single-dose vial (no preservative).

Abbreviations: MAP, microarray patch; RSV, respiratory syncytial virus.

Optimal product pair 7: Hepatitis C + dry-powder respiratory delivery

Technology overview

- Dry-powder respiratory delivery technologies are needle-free, improve thermostability, deliver vaccine directly to the mucosa, and induce both systemic and mucosal immunity.
- Particularly useful for hepatitis C because vaccine is delivered directly to the mucosal surfaces, which is the site of mother-to-transmission.

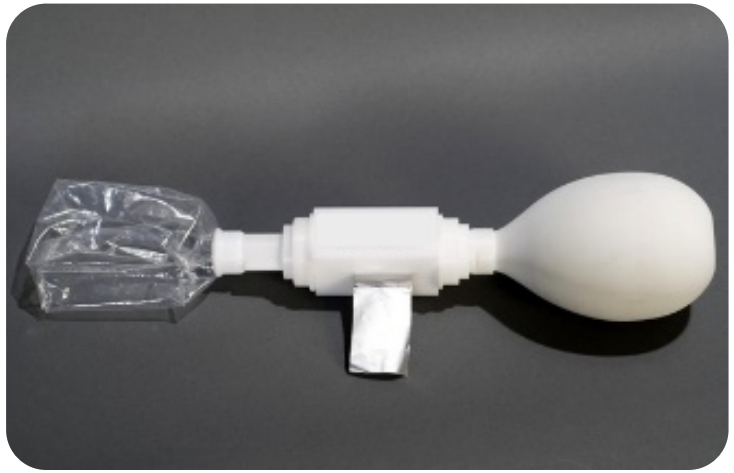


Photo: AKTIV-DRY

Feasibility summary

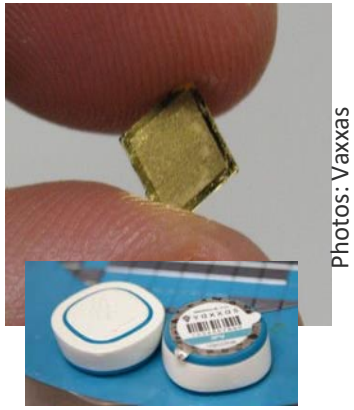
- Technical feasibility: Although dry-powder respiratory delivery for hepatitis C vaccine is possible based on the pathogen and natural route of infection, no candidates currently exist.
- Programmatic feasibility: Dry-powder respiratory delivery can shorten wait times, optimize doses per container, increase cold chain flexibility, reduce sharps waste, reduce glass waste, enable task-shifting to minimally trained health workers, and have robust packaging.

Current presentation: Assumed to be liquid vaccine in single-dose vial (no preservative).

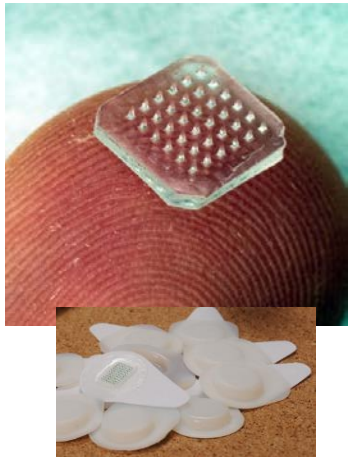
Optimal product pair 8: Hepatitis C + MAP

Technology overview

- Patches consist of hundreds of tiny projections that deliver solid vaccine into the skin. Some platforms require an applicator for delivery (integrated or separate).
- Potential for enhanced thermostability (controlled temperature chain use) and controlled-release delivery (schedule reduction).



Photos: Vaxxas



Photos: Georgia Tech

Feasibility summary

- Technical feasibility: MAP delivery of a hepatitis C vaccine has been tested in a preclinical study in mice immunized with a DNA vaccine encoding hepatitis C virus NS3/4A protein-coated MAP. The hepatitis C MAP induced a NS3/4A-specific cytotoxic T lymphocyte response in mice, which suggests the potential for a hepatitis C DNA–coated MAP to induce a cellular immune response.*
- Programmatic feasibility: MAP delivery can reduce preparation time, shorten wait times, optimize doses per container, increase cold chain flexibility, reduce sharps waste, reduce glass waste, minimize training/literacy requirements, enable task-shifting to minimally trained health workers, and minimize weight and bulk. It also can have robust packaging.

* Gill HS, Sõderholm J, Prausnitz MR, Sällberg M. Cutaneous vaccination using microneedles coated with hepatitis C DNA vaccine. Gene therapy. 2010;17(6):811-814.

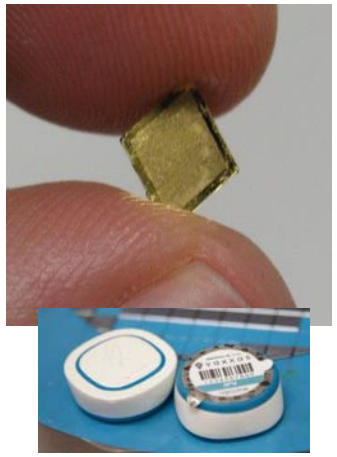
Current presentation: Assumed to be liquid vaccine in single-dose vial (no preservative).

Abbreviations: DNA, deoxyribonucleic acid; MAP, microarray patch; NS, nonstructural.

Optimal product pair 9: Dengue + MAP

Technology overview

- Patches consist of hundreds of tiny projections that deliver solid vaccine into the skin. Some platforms require an applicator for delivery (integrated or separate).
- Potential for enhanced thermostability (controlled temperature chain use) and controlled-release delivery (schedule reduction).



Photos: Vaxxas

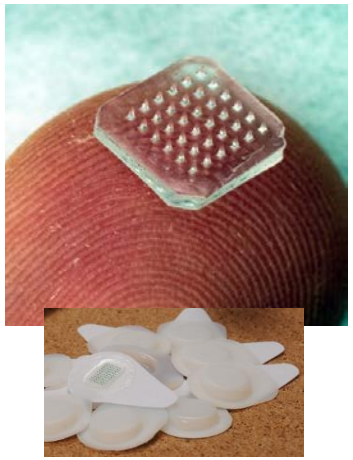


Photo: Georgia Tech

Feasibility summary

- Technical feasibility: MAP delivery of a dengue vaccine has not yet been demonstrated in preclinical studies in animals or clinical trials in humans.
- Programmatic feasibility: MAP delivery can reduce preparation time, shorten wait times, optimize doses per container, increase cold chain flexibility, reduce sharps waste, reduce glass waste, minimize training/literacy requirements, enable task-shifting to minimally trained health workers, and minimize weight and bulk. It also can have robust packaging.

*Carey et al. (2014)

Current presentation: Assumed to be liquid vaccine in single-dose vial (no preservative).

Abbreviations: MAP, microarray patch.

Conclusion

- Dry-powder respiratory delivery, sublingual delivery, and MAPs offer the greatest promise for reducing barriers to delivery of maternal vaccines in the future.
- ID needle-based technologies, ID DSJIs, BFS containers, CPADs, liquid respiratory delivery, and SC/IM DSJIs also offer some advantage over current packaging and delivery methods.
- In many cases, the most promising pairings would also be the most technically challenging to develop and manufacture, and they have a lower probability of technical and regulatory success. In-depth review and research are needed to assess technical feasibility of the selected pairings.
- It is increasingly difficult to introduce a new vaccine delivered through a novel technology in a vulnerable population like pregnant women. Extensive safety data will be required and a new vaccine delivered through standard needle and syringe would likely reach pregnant women in need faster than a novel packaging or delivery technology.
- Further evaluation would also be needed to characterize the potential total cost and health impact a particular technology pairing could have on country-level maternal immunization.

Abbreviations: BFS, blow-fill-seal; CPAD, compact, prefilled, autodisable device; DSJI, disposable-syringe jet injector; ID, intradermal; IM, intramuscular; MAP, microarray patch; SC, subcutaneous.