

## Section A. Cover page

### 1. Title

Using novel packaging and delivery technologies to improve access to adult vaccines in low-resource settings

### 2. Abstract

The scope of adult immunizations in many developing countries currently centers on a handful of vaccine-preventable diseases, but these vaccines have had limited reach within their target populations. Under this work, we will conduct an assessment of adult immunization-delivery scenarios in both low- and middle-income countries, with a focus on maternal immunizations. We will examine market requirements, program priorities, and user needs. We will identify possible constraints that may limit coverage of existing and future adult vaccines and map selected constraints to innovative packaging and delivery technologies that may help to optimize adult, particularly maternal, vaccine coverage. We will work with a variety of individual experts, but do not anticipate pursuing institutional collaborations. Instead, we will leverage the strength of PATH's network of country offices to conduct the needs assessment.

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## **Section C. Main section of the proposal**

### **3. Overall goal and objectives**

#### *Goal*

To improve the health of adults in low- and middle-income countries (LMICs) through increased access to adult, and particularly maternal, vaccines by identifying packaging and delivery options that address market requirements, program priorities, and patient and provider needs.

#### *Objectives*

1. Determine current state of the market for adult immunizations and assess stakeholder requirements (six countries).
2. Characterize adult immunization delivery scenarios, with a focus on maternal immunization, and identify constraints to increased coverage (two countries).
3. Map packaging and delivery technologies to address requirements and constraints identified under Objectives 1 and 2.

### **4. Technical approach**

#### *Introduction*

In recent years, alongside rising investments in childhood immunization in low-resource settings, there has also been an increased focus on expanding the use of all vaccines, including those targeting adult populations.<sup>1</sup> Factors influencing a greater need for adult immunizations include global pandemics, an increased focus on accessing high-risk groups such as pregnant women, an aging demographic, and a more interwoven global population. In spite of increasing momentum, the scope of adult immunizations in many developing countries currently centers on a handful of vaccine-preventable diseases, such as tetanus, influenza, meningitis A, and rabies.<sup>2</sup> Overall, many of these vaccines have had limited reach compared to the breadth of their target populations, yet it is widely recognized that vaccines are one of the most cost-effective approaches to reduce global disease burden.<sup>3</sup>

For the past 25 years, PATH has endeavored to increase access to vaccines with a breadth of approaches, including 1) technology innovations such as vaccine vial monitors (VVM) and the Uniject™ injection system, 2) advancing new and underutilized vaccines such as meningitis A and malaria, 3) and strengthening immunization systems through programmatic collaboration with governments, the World Health Organization (WHO), the United Nations Children’s Fund (UNICEF), the GAVI Alliance, and other partners. We have continued to expand our immunization work in new areas, with a focus on improving the health of women and children. PATH recognizes the global health importance of adult vaccines, particularly for pregnant women, who are specifically targeted by the WHO recommendations for adult immunization. We have programs aimed at developing new maternal vaccines, such as RSV, and increasing access in maternal populations to existing adult vaccines, such as influenza. Our effort is mirrored by a growing focus among the global health community to expand access to maternal immunizations, conferring protection of infants from maternal antibodies. For example, WHO is

building the maternal tetanus vaccine initiative into a robust platform to prevent infections among women and infants.<sup>4</sup> In addition to some other upstream vaccines, pneumococcal, *Haemophilus influenzae* type B, and pertussis vaccines are used widely among certain populations and could be added to this maternal health platform.

In addition to maternal vaccines, several groundbreaking vaccines that could dramatically shift the structure of adult immunization programs are in development. In particular, vaccines for AIDS, malaria, tuberculosis (TB), and dengue may be integrated into existing public health programs in the near future.

Whether in use or in the development pipeline, for vaccines to reach their target populations, vaccine manufacturers, program managers, and global immunization program leaders must have a foundation of evidence detailing the contexts of adult vaccination, barriers to achieving maximum coverage, and the potential shifts with new vaccine introduction.

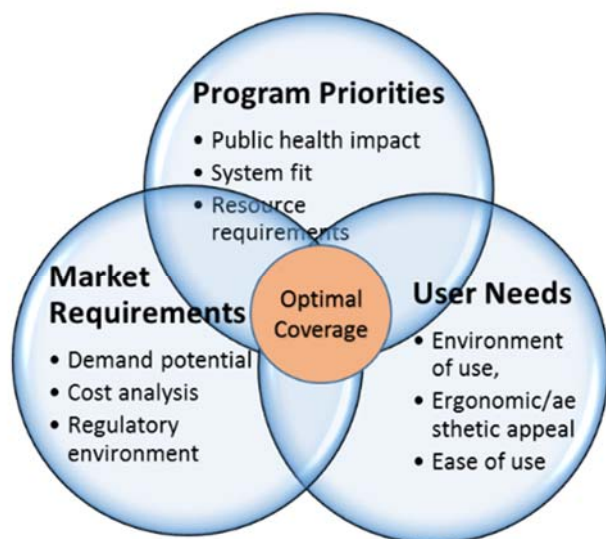
#### *Current assessment of need*

The lessons learned from successful childhood immunization programs have highlighted the importance of appropriate packaging and delivery options for maximizing immunization coverage.<sup>5</sup> 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.<sup>6</sup> This expansion reflects efforts to improve systems for managing the procurement, storage, transport, and delivery mechanisms for childhood immunization. For example, improved cold chain equipment, thermostable vaccine formulations, and the introduction of VVMs enabled facilities previously considered to be on the periphery of the immunization system to routinely stock and deliver vaccines to rural populations. Likewise, combining vaccines into multivalent formats has reduced the work burden for health care providers and reduced the number of times a patient must visit and time spent at the clinic, and single-dose packaging, prefill and auto-disable syringes, and ID syringe adapters have reduced training requirements and risks to the health care worker and the surrounding communities, enabling minimally trained providers to deliver certain vaccines. More recently, ID adapters, microneedle patches, and disposable-syringe jet injectors have been developed to 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 designed to address constraints unique to delivering vaccines to children in LMICs. Rabies vaccine, delivered to adults, illustrates the potential for innovative delivery mechanisms. Vaccines for rabies are often expensive and limited in supply. Rabies vaccine is not universally administered by the intradermal (ID) route, a difficult technique to master using a traditional needle and syringe. Yet using ID delivery, 60 percent less rabies vaccine is used in the modified Thai Red Cross ID schedule compared to the Essen IM schedule. If a delivery device expands the set of health care workers that can provide ID injections as opposed to intramuscular (IM) shots, it will reduce the total amount of vaccine required to immunize a population, thereby reducing costs. Alternative delivery devices have the potential to reduce the training requirements and improve efficacy of delivery of the reduced ID volumes. For adult immunization programs to reach scale and achieve broader

health impact, manufacturers and immunization program managers may wish to identify where preemptively optimizing the packaging and delivery of their vaccines may contribute to increased uptake.

Optimal vaccine coverage is most successful when a vaccine's product attributes complement the delivery scenario. Examples of product attributes that may impact coverage include packaging, storage requirements, delivery mechanism, delivery schedule, and price; delivery-scenario elements include market structure, regulatory environment, programmatic priorities, and end-user needs. The figure below illustrates the intersection of these components around vaccine coverage.



As adult immunization programs continue to scale up, and new adult vaccines become available, it will be important to have a detailed understanding of the relationship among these elements, including points of friction that may constrain successful uptake. We therefore propose an assessment to identify priority adult vaccines, particularly those with maternal health impact, describe their market requirements, program priorities, and patient and provider needs, identify barriers to optimal coverage, and propose technology solutions that may maximize vaccine coverage.

#### Unique requirements of adult immunization

In LMICs delivery scenarios for adult vaccines may differ from those of childhood immunization other than for routine maternal vaccination. The target markets for adult immunization in LMICs can be broadly categorized into the private and public sectors. Depending on the country, these sectors may share or have different supply chains, logistics, procurement processes, human resources capacity, training requirements, and patient populations. To optimize vaccine delivery to address the unique constraints of adult immunization programs, we propose an assessment of the programmatic priorities, environments of use, health care provider needs, patient preferences, and supply logistics. Our primary focus will be on maternal immunizations in the public sector, but we will also include a high-level assessment of the

private sector, where it is active. This reflects PATH's approach in achieving widespread public health impact in low-resource settings by developing appropriate technologies and advancing markets to meet a broad spectrum of needs. Uptake of adult immunization in the lowest resource settings will be spurred to the extent the purchase power of the private sector in higher resource countries is leveraged to bring products to scale, encourage higher-capacity production, and lower costs.

#### Challenges delivering adult vaccines in LMICs

Vaccines for low-resource settings have the tremendous challenge of needing to be affordable, stable, easy to deliver, have a long shelf life, and low-volume packaging.<sup>7</sup> Vaccines most commonly given to adults in low-resource settings include:

- **Influenza A.** Vulnerable populations, including pregnant women, are recognized as being at high risk for influenza-associated complications, and they are recommended to receive annual influenza vaccine in the United States.<sup>8</sup> Likewise, during the H1N1 (hemagglutinin 1 neuraminidase 1) pandemic, pregnant women were identified as a priority group for receipt of vaccine by WHO and national policy committees.<sup>9,10</sup> In the only randomized clinical trial assessing trivalent influenza vaccine effectiveness among pregnant women and their newborn infants in Bangladesh, researchers demonstrated significant reductions in respiratory illness among both mothers and infants.<sup>11</sup> Vaccinating pregnant women could facilitate adoption of a strategy which could have significant impact in decreasing influenza-associated maternal and neonatal disease.
- **Tetanus toxoid.** While tetanus rates are decreasing overall, public health programs are considering the benefit of linking EPI and maternal health efforts to protect both pregnant women and their infants. This concept of a maternal vaccine platform could offer protection against a variety of diseases such as tetanus toxoid, pertussis, and influenza for up to six months of age through the effects of maternal antibodies.
- **Meningococcal.** Introduction of the new meningitis A vaccine, MenAfriVac<sup>®1</sup> in 2010, through the Meningitis Vaccine Program (MVP), provides a model for innovation that allowed an estimated 150 million people to be reached by the end of 2013. Currently, 1- to 29-year-olds receive the vaccine, though the expectation is to shift delivery to routine EPI administration within the next five years.<sup>12</sup> MVP obtained regulatory approval for the vaccine, which is heat-stable, to be stored in a controlled temperature chain (in Burkina Faso), allowing even greater reach.<sup>13</sup>

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<sup>1</sup> MenAfriVac<sup>®</sup> is a registered trademark of Serum Institute of India Ltd.

- **Rabies.** More than 10 million people receive rabies vaccine annually, the majority of whom are in regions of the developing world, where the disease is endemic.<sup>14</sup> Vaccines for rabies are often expensive and limited in supply, though in high demand. Use of ID delivery has been limited, as programs have been hesitant to take on a disruptive practice despite the clear cost benefits.

### Country selection

We will select six countries from among the following where PATH has a country presence or partners in the immunization sector: African Region—Kenya, Senegal, South Africa, Tanzania; South East Asia Region—India, Thailand; Western Pacific Region—Vietnam, China; Pan American Region—Peru, Brazil. This initial list of possible countries was selected because it comprises countries with a diversity of immunization scenarios, the presence of a PATH office or strong collaborating partner, PATH experience and connections with the countries' immunization programs, and where at least one adult vaccine is provided through the public sector, with several countries, namely Brazil, India, and China, that have more established adult vaccination strategies than their lower-resource counterparts. A final selection of six countries from the full list will be identified to participate in a survey of key stakeholders. The final six countries will be selected based on how well their health systems reflect the condition of others within their regions, PATH's ability to rapidly connect with relevant key stakeholders through network sampling, and the potential to leverage opportunistic travel to the country. We will also consider the existence of a strong private sector for provision of adult health care.

While data collected from the six countries will provide valuable insight into the market drivers for adult vaccines in LMICs, to create a comprehensive picture of the factors at play and barriers to optimal coverage, a country-level assessment of the delivery scenarios for maternal and other adult vaccines will be necessary. From the six countries selected for the global survey, we will down-select two countries to conduct case studies of the adult immunization-delivery scenarios and identify possible barriers to optimal coverage.

The down-selection criteria will include programmatic relevance and pragmatic viability. The selection process will align with PATH's focus on women's health in low-resource settings by including one low-income country with a public-sector antenatal care program representative of other low- or middle-income countries; and one middle-income country that includes a robust private-sector for delivery of adult vaccines, particularly for pregnant women, and which is representative of other low- or middle-income countries.

If possible, we will select countries from different WHO regions, but the priority will be given to countries identified in Objective 1 with a higher burden of vaccine-preventable diseases, clear opportunities to integrate maternal immunization into existing antenatal care programs, evidence of market potential, and country engagement allowing rapid ramp-up of activities.

### Target audience

The outcomes of this analysis will ultimately serve the adult populations who will benefit from widespread uptake of adult vaccination. In particular, those individuals who are in high-risk

groups, such as pregnant women (and their infants through maternal antibodies), immunocompromised individuals such as those living with HIV, health care workers, and the elderly may benefit from increased access to priority vaccines. Pandemic settings will also be considered.

More immediately, the results of the assessment and mapping exercise will offer immunization program managers, vaccine manufacturers, and technology developers a valuable foundation of evidence to support program planning, market decisions, and vaccine-development efforts. At the Next-Generation Vaccine Delivery Technology Meeting convened by WHO in February 2014, technology developers requested assistance with identifying public health needs and priorities, quantifying potential impact, influencing purchasers' decision-making processes, and meeting the shifting and uncertain regulatory requirements. Technology and vaccine developers also seek consultations from the public sector on specific technologies and product attributes as well as technical, laboratory, human factors, and field evaluations of their technologies. These developers often do not have the facilities or linkages with developing-country ministries of health to conduct such studies and would benefit from these findings. In addition, WHO, multinational vaccine manufacturers, and other global-level stakeholders have expressed interest in increasing the involvement of product-development groups and developing-country vaccine manufacturers in the Vaccine Presentation and Packaging Advisory Group (VPPAG).

The evidence base established by the work proposed here can foster collaborative dialogue among these parties and help to ensure that efforts to advance specific solutions and target product profiles for vaccine products and new technologies are driven by country needs and evidence drawn from the intended scenarios of use.

#### *Project design and methods*

We will conduct this work through seven activities aligned with our three project objectives.

#### Objective 1. Determine current state of the market for adult immunizations and assess stakeholder requirements (six countries).

Our deliverable for Objective 1 is a report on market requirements, program priorities, and priority vaccine attributes.

**Activity 1. Define public health and programmatic priorities in six countries.** Global burden of disease data will be captured for vaccine-preventable diseases affecting adults in LMICs, particularly women, focusing primarily on the six target countries. We will conduct desk research and interview key global stakeholders including those from PATH's vaccine access, delivery, formulation, supply chain, and technology innovations, to understand public health and program priorities for maternal and other adult vaccines, immunization-delivery scenarios, trends, and desired product requirements. This will be done through a combination of desk research and interviews with key stakeholders from the six countries. We will look at country data to understand which diseases are increasing and which are decreasing, and identify major causes of adult mortality for which vaccines are under development (i.e., malaria, AIDS, and TB). Although our lens will be focused on existing vaccines, it will be valuable to understand

how country stakeholders prioritize the existing adult vaccines alongside vaccines in the development pipeline. We will identify successful experiences in reaching adults with health (or other) interventions in the six countries. Relevant lessons learned from increasing coverage for EPI delivery in the six countries will also be captured. We will conduct the interviews in person where feasible, using PATH or partner staff in country. We will leverage funded PATH travel to priority countries to conduct the interviews in person. Alternatively, interviews will be done by telephone.

**Activity 2. Landscape of commercially available and pipeline vaccines for adults.** To determine program priorities for maternal and other adult vaccines, we will conduct desk research and structured interviews among key global stakeholders from WHO, UNICEF, GAVI, nongovernmental organization (NGO) partners, and industry to identify the landscape of existing adult vaccines and their priority. Through our desk research, we will identify commercially available vaccines for adults marketed in LMICs. Interviews will be by telephone or by leveraging PATH staff travel to countries. We will identify priority adult vaccines and those in the pipeline. Questions will include current vaccine program status, needs, requirements, and constraints.

**Activity 3. Describe market requirements for selected vaccines.** We will assess WHO and national-level market requirements and demand potential for selected maternal and other adult vaccines in the six target countries. When possible, regulatory requirements both at the level of WHO prequalification as well as national regulatory authority requirements will be identified. We will work to determine if a selected country has representation in the International Medical Device Regulators Forum and locate the name and contact information for those country-level contacts for interview and information gathering.

In addition, the characterization of the public- and private-sector procurement channels for importation and use of these vaccines will occur. Segments of the adult population will be assessed and categorized in terms of health need and vaccine access. In particular, maternal immunization program efforts or needs and requirements will be determined, as well as adults at special risk (elderly, immunocompromised individuals, health care workers, individuals working with livestock). Identification of individual NGO or aid agency efforts focused on improving vaccine access for use in adult immunization will be conducted, to determine potential alignment and further engagement during Objective 2 project activities.

Objective 2. Characterize adult immunization delivery scenarios, with a focus on maternal immunization, and identify constraints to increased coverage (two countries).

The deliverable for Objective 2 will be a report on delivery scenarios and barriers for adult vaccines in LMICs.

**Activity 4. Describe programmatic constructs, constraints, and barriers for maternal and other adult vaccination in two countries.** We will down-select to two of the six original countries for this objective (see country selection section for down-selection process). Desk research will explore published and grey literature on the public health structures for vaccine delivery to adults in the two target countries, with a focus on antenatal care settings. In-depth interviews



with key country stakeholders, including Ministry of Health (MOH), EPI, WHO, GAVI, UNICEF, and NGO partners will be used to identify challenges for adult vaccination. Key stakeholders will include EPI managers, procurement and supply chain representatives, and experts in advocacy and behavior change communications. We will explore private-sector vaccine delivery for adults, where there is a vibrant private sector.

Lines of inquiry will include policies; current and future adult vaccines; where, when, and how vaccines are delivered; challenges and opportunities in reaching adults; health systems; missed opportunities; and barriers. Procurement and distribution channels for public-sector vaccines will be explored. We will learn how adult vaccines fit with the EPI supply chain, whether there is a push or pull system by which to procure these vaccines, and which actors are responsible for ensuring their availability. We will determine if they are all stored in the cold chain or if some are heat-stable and able to be stored in a controlled-temperature chain. Factors related to vaccine packaging, presentation, and route of delivery will be discussed with MOH and EPI staff, including clinicians.

**Activity 5. Describe regulatory environment for new and existing vaccines and delivery technologies.** The regulatory pathway for vaccines can be challenging from both a resource perspective as well as a timeline perspective. Routinely, vaccine developers require several years to conduct the studies necessary and obtain regulatory approval within the country of origin (manufacture) and the country of use, as well as to successfully obtain WHO prequalification, which is a prerequisite for UNICEF tender and procurement.

In addition, any variation of a vaccine presentation after licensure and approval represents additional regulatory review and approval process. This would include changes in manufacturing, formulation, and packaging or delivery method. This regulatory process can also take multiple years and represent a challenge in terms of resource requirements and overall time required.<sup>15</sup>

As noted by participants of the Next-Generation Vaccine Delivery Technology Meeting convened by WHO in February 2014, a common challenge is the regulatory process required to both obtain approval for the vaccine as well as the alternative packaging or delivery technology. There is currently a lack of clarity on the alignment among regulatory bodies regarding the requirements for new presentations or methods to deliver vaccines. As reported during the WHO meeting, 65 percent of countries report having an agency capable of regulating medical devices. Many of these same agencies are in different stages of development.

The project team will determine the regulatory bodies responsible for new vaccine presentations and delivery technologies, while also finding opportunities to engage in a dialogue with country-level personnel on 1) potential vaccines in the pipeline for adult immunizations; and 2) existing or new vaccine technologies that might be suitable for such vaccines near- or long-term. We will work to determine what the regulatory requirements might be through interview and desk-based research. While an actual filing would provide more specific information in terms of the regulatory requirements and regulatory body perspective, our findings will still form a basis of understanding to inform decision-making.

**Activity 6. Describe provider needs and patient preferences.** A final element of characterizing the delivery scenarios for maternal and other adult vaccines is the study of the environments of use for the vaccines and the needs and preferences of the end-users. Environment of use may vary by vaccine, country, and location. A successful vaccine will have packaging, storage, and delivery modes that meet the needs of both the minimally trained health worker at an outpost clinic or a nurse at a referral hospital. The resources available to the users in these two settings, the robustness of infrastructure, the number of patients seen in a day, and the population epidemiology may be very different in these two environments of use, and a successful vaccine will meet the requirements of both environments of use.

The spectrum of potential environments of use and types of users must be well-characterized to understand potential barriers to coverage in the delivery setting. We will therefore conduct rapid assessments in two countries, consisting of in-country interviews and contextual inquiry to define the environments of use for priority vaccines, and to explore the needs of the end-users—the supply chain managers procuring and delivering vaccine, the health care providers delivering vaccines, and the patients receiving vaccines.

In-country rapid assessments will consist of interviews with three to five key stakeholders in the operational levels of the national immunization systems, and visits to two to four delivery settings to observe the environment of use at the point of delivery and to probe/interview health care workers in those settings. For the purposes of patient privacy, patients will not be interviewed directly, but patient perspective will be gained through discussion with the health workers who care for them.

Without careful analysis, the barriers within the market, immunization programs, and delivery settings may undermine efforts to achieve optimal coverage. Drawing from the data collected during the market assessment and in-country rapid assessment, we will conduct an in-depth qualitative analysis of the data to identify potential gaps that could impede coverage and uptake of various vaccines, as well as other opportunities to optimize vaccines for ease of delivery and acceptability to patients and providers. Analysis will be conducted in several modes: data coding using qualitative data analysis software, group vetting exercises within PATH's Vaccine and Pharmaceutical Delivery Technologies (VPDT) portfolio to discuss initial outcomes, and follow-on correspondence with the in-country key stakeholders to collect further details on specific constraints and validate findings of the constraints-identification exercise.

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

Our Objective 3 deliverable is a final report and matrix of vaccines, barriers, and possible technology solutions.

**Activity 7. Map packaging and delivery technologies to address requirements and constraints.**

The data collected during the activities described under Objective 1 will offer a global view of market requirements, program priorities, and stakeholder priorities, and Objective 2 will provide a more detailed analysis of maternal and other adult immunization scenarios in two

case-study countries. Drawing from this evidence base, VPDT will engage in a series of mapping exercises to view the relationship of vaccine presentations to target market segments, potential environments of use, provider needs, patient priorities, and supply logistics to identify opportunities to optimize delivery of vaccines with alternative packaging and delivery technologies. VPDT houses a staff of experts in the translation of innovative vaccine packaging and delivery technologies into solutions to meet the unique requirements of LMIC immunization scenarios. We will begin by selecting the top-priority adult vaccines as illustrated under Activities 1 to 3, and mapping these vaccines to the existing and, where possible, potential packaging and delivery presentations available. We will then catalog the requirements for each vaccine—market, regulatory, programmatic, and environment of use—and compare these requirements to the vaccine attributes. Finally, we will select from the constraints identified in Objective 2 those barriers that may be addressed by technology solutions, existing or in development, and map these solutions to the paired attributes and requirements.

Many of the key outcomes of this work will highlight constraints related to regulatory or market requirements, or program-development opportunities. Pursuing these avenues of inquiry will be an important next step for vaccine manufacturers and program managers seeking to optimize global strategies for increasing vaccine coverage and will require further dedicated resources to support that effort.

### Methods

As described under the activities above, to ensure the resulting evidence base is representative of the larger global adult-immunization picture and offers a breadth and depth of detail, we will employ a mix of desk research, electronic surveys, in-depth interviews by telephone and in person, contextual inquiry, and several modes of qualitative analysis.

**Literature reviews and other desk research.** The team will conduct desk research at the initiation of the project to inform the design and direction of the global-level stakeholder survey and vaccine-prioritization activities. The research will include literature reviews to identify existing areas of work related to process improvements for maternal and other adult immunization, previous studies related to priority vaccines for LMICs, existing and potential adult vaccines of interest and their primary attributes, and identify key stakeholders for the global stakeholder survey. We will also begin to describe the relevant market forces and regulatory requirements, and initiate a network sampling process for selecting key informants. This work will establish a framework for the contextual inquiry and stakeholder interviews to be conducted later in the project.

**Electronic surveys.** An open-ended survey of limited scope and length can be a highly effective method for quickly collecting a breadth of data on a specific subject. We will survey in-country experts from six countries (to be determined) and global stakeholders using open-ended email or online surveys. The initial results from these surveys will inform project direction at its onset, and subsequent iterations with narrower scope will be sent to a broader sample of stakeholders in order to refine lines of inquiry. The content of the surveys will vary depending on the stakeholder, exploring issues related to market requirements, priority public health issues and corresponding vaccines, country program priorities and constraints, global experts'

priorities, and known barriers to optimal vaccine coverage. The iterative approach to the surveys, and the topic-specific construct, will enable the group to achieve breadth of generalizable data, depth of detailed examples, and consensus within groups of stakeholders on specific topics.

**In-depth interviews.** In-depth interviews will focus on key stakeholders at the country level, at both the higher program levels, and in the lower tiers of the selected countries' immunization systems (public and private). Stakeholders interviewed at the program level will be able to offer insight into the country-specific adult immunization program structure and constraints, while stakeholders at the operational levels will have relevant expertise related to implementation of adult vaccination, such as supply chain managers, regional program managers, and facility managers. They will be best able to identify the types of constraints that can temporarily derail the smooth functioning of a supply chain or delivery strategy. Up to four program-level stakeholders, and another six mid-level stakeholders in each country will be identified by a network sampling method, based on connections established at the time of the global survey under Activity 1.

**Contextual inquiry.** Contextual inquiry is the combination of observation of the informant in his or her own environment combined with targeted questioning or interviews based on the observations of the qualitative researcher. In this project, contextual inquiry will take place at the point of adult vaccine delivery, to gain a deeper understanding of where the vaccines will ultimately be delivered, the levels of infrastructure available, the material and human resources available, who receives them, and the motivations of the various actors in this environment of use. These details often inform not just product-design decisions, but also provide key insight into the ultimate drivers of demand of vaccine—access to the target population, and desire (self-motivated or enforced) of the target population to be vaccinated. As part of the network sampling process described above, we will identify three to five locations in each country representing what the key stakeholders identify as differing types (existing and potential) of environments of use for maternal and other adult vaccines. We will spend several hours in each location observing and probing with targeted questions the health workers delivering the vaccine.

**Qualitative analysis.** We will employ several qualitative data-analysis methods in order to extract relevant detail from the various sources of data. Primarily, the bulk of the data from these activities will be limited to coding and theme sorting, inductive summarization, and affinity diagramming. Each of these methods enables an alternative view of the same data, helping extract meaning while minimizing bias in analysis.

**Mapping exercises.** Finally, the team will engage in a series of mapping exercises to view the relationship of vaccine presentations to target market segments, potential environments of use, provider needs, patient priorities, and supply logistics to identify opportunities to optimize delivery of vaccines with alternative packaging and delivery technologies.

### *Evaluation design*

This activity will establish a foundation of evidence for optimization of adult vaccination efforts, but will have no immediate impact on vaccine coverage or related health outcomes. Rather, it creates a body of evidence that has not been captured to date. As such, baseline metrics offer little meaningful data for comparison, as these data may only be used in tenuous comparisons and broad extrapolations. Instead the deliverables of this work will be evaluated against the indicators of the project logical framework (Appendix 1) which will be refined at the end of Activity 1. The deliverables will be reviewed by an expert advisors consisting of global-level vaccine-delivery and -introduction experts, as well as the in-country stakeholders who will provide data validation through source confirmation.

### Evaluation indicators

At the completion of the project, we will have:

- Created an action plan with key stakeholders to address the barriers identified during the assessment.
- Identified priority vaccines in collaboration with in-country and global stakeholders.
- Identified priority public health and programmatic issues in collaboration with in-country and global stakeholders.
- Described market requirements for selected priority vaccines.
- Created detailed descriptions of maternal and other adult immunization-delivery scenarios.
- Identified barriers to optimal coverage for all scenarios.
- Proposed packaging and delivery technology solutions for a subset of selected barriers.

## **5. Detailed work plan and deliverables schedule**

This activity will span two years and will include research in a total of six LMICs. There are three objectives which will occur sequentially (see Appendix 2).

**Objective 1.** Determine current state of the market for adult immunizations and assess stakeholder requirements (six countries).

This objective will occur in months 1 to 8 and will involve desk research and liaising with country stakeholders through in-person interviews. PATH staff from headquarters and country programs with expertise in vaccination systems and delivery technologies will identify high-level staff and invite participation. Our staff will develop the study design and tools and obtain approvals to conduct the research from PATH's Research Determination Committee and any country approvals required. Where possible, in-country PATH staff with an immunization background will conduct the in-person structured surveys or, alternatively, we will leverage PATH staff in Seattle (PATH's headquarters) who are traveling to the country. Any travel in this first objective will be opportunistic. Where necessary, we will hold telephone interviews. Data will be cleaned and analyzed by PATH for all six countries. The deliverable, a report on adult vaccine market requirements, will be completed by month 8.

**Objective 2.** Characterize adult immunization delivery scenarios, with a focus on maternal immunization, and identify constraints to increased coverage (two countries).

The second objective will occur from months 7 through 16. In this objective, we will review programs, policies, practices, and supply chains for adult vaccines as captured in the Objective 1 report. From this analysis, we will down-select to two countries for a deeper focus. PATH will develop in-depth interview guides for the various target audiences building off the findings from Objective 1 to identify maternal and other adult vaccination scenarios and constraints. Interviews will be conducted primarily by country staff. The public health expert will make one trip per country near the end of year 1 to lead the contextual inquiry and provider research. Data will be analyzed by PATH. The deliverable will be a report on delivery scenarios and barriers to adult vaccination. It will be completed by month 16.

**Objective 3.** Map packaging and delivery technologies to address requirements and constraints identified.

This objective will take place from months 16 through 24. This will be desk-based work carried out by PATH. No travel is funded for this phase of the work. Priority adult vaccine requirements and markets will be mapped against enabling vaccine packaging and delivery technologies to address identified requirements and constraints. We will disseminate findings through PATH's website, with VPPAG, and by sharing with TechNet and posting on other relevant websites. The deliverable will be a final report with a matrix of adult vaccines mapped to packaging and delivery technologies, which will be completed by month 24.

## Section D. Organizational detail

PATH is an international organization that drives transformative innovation to save lives and improve health, especially among women and children. We accelerate innovation across five platforms—vaccines, drugs, diagnostics, devices, and system and service innovations—that harness our entrepreneurial insight, scientific and public health expertise, and passion for health equity. By mobilizing partners around the world, we take innovation to scale, working alongside countries primarily in Africa and Asia to tackle their greatest health needs. Together, we deliver measurable results that disrupt the cycle of poor health.

The Vaccine and Pharmaceutical Technologies Group (VPTG) at PATH focuses on the development of tools and methods that improve safety, acceptability, and effectiveness of immunization and drug delivery. Our research explores the experiences of all the stakeholders in the value chain in an effort to understand their needs and constraints as well as collect their feedback on ideal product attributes. We use these data to work with developers and manufacturers to create or adapt technologies to fit the conditions of use. VPTG is involved with the design and assessment of primary container technologies such as prefilled syringes, blow-fill seal, oral droppers, integrated reconstitution technologies, and alternative delivery technologies such as microneedle patches, intranasal delivery, and needle-free jet injectors to improve access and delivery. The team has experience in device regulatory processes both domestically and internationally. This has included standalone devices as well as combination products and involved the development of regulatory strategy for a number of different technologies.

Our work in these areas began with the development of the vaccine vial monitor and autodisable syringe technology more than 30 years ago and has expanded to a broad portfolio of work to improve vaccine products and delivery technologies. Now, as a global leader in the areas of vaccine products and technologies for developing-country markets, we are routinely contacted to provide input on new technologies and their suitability for use in global public health. PATH currently chairs the VPPAG, leads the working group on the generic preferred product profile, and contributes to the working groups on decreasing the volumes of vaccine containers and barcoding. Additionally, as a member of WHO Immunization Practices Advisory Committee, we frequently advise WHO on policy and technical issues and assist WHO with prequalification issues related to vaccine products and delivery devices.

PATH has a long history of active engagement with private-sector partners to evaluate and advance a variety of vaccine technologies. PATH has worked with many of the key global vaccine technology developers and manufacturers, including BD, West Pharmaceutical Services, Rommelag, Lameplast, Harro Höfliger, Aptar Pharma, Terumo, Star Syringe, Crucell, GeorgiaTech, University of Queensland (Vaxxas), NanoPass, Corium, Merck, Inovio, PharmaJet, and Bioject (among others).

In addition to technology development, PATH is working toward a world where the most vulnerable people are protected from devastating diseases through increasing equitable access to lifesaving vaccines. Our Vaccine Access and Delivery program works to ensure optimal

uptake of vaccines in some of the world's most challenging settings. Dedicated teams work on a range of vaccines, including those that protect against diarrheal disease, pneumonia, and Japanese encephalitis, as well as other new and underused vaccines.

PATH is also a lead partner in the Accelerated Vaccine Introduction (AVI) initiative. Launched by the GAVI Alliance, AVI unites scientific, public health, policy, and management expertise to help national governments address all aspects of successful immunization, including vaccine procurement, policies, financing, training, logistics, and delivery.

**PATH's global presence.** With offices in 21 countries and projects in more than 70 countries, PATH is closely linked with ministries of health and has infrastructure to support project needs. As previously mentioned, our short list of potential countries for this proposed grant includes:

- African Region—Kenya, Senegal, South Africa, Tanzania.
- South East Asia Region—India, Thailand.
- Western Pacific Region—Vietnam, China.
- Pan American Region—Peru, Brazil.

Specifically, PATH has worked with many countries in the areas of vaccine products and delivery technology; for example, conducting market research on vaccine product attributes in Brazil, China, India, Peru, Philippines, and Tanzania; evaluating costs to introduce disposable-syringe jet injectors in Brazil, India, and South Africa; and conducting human factors or usability evaluations of vaccine-delivery technology designs in China, India, Senegal, South Africa, and Tanzania. These evaluations required close interactions and planning with ministries of health and other country stakeholders to ensure successful completion of the research and subsequent reporting of results.

**Facilities.** PATH has a 6,000-square-foot product development and testing facility that has steadily increased in capability over the past 25 years. PATH's product-development shop is divided into a machine shop, model shop, product and environmental testing bay, and microscopy laboratory.

PATH's multipurpose biosafety level-2 laboratory is equipped to produce liquid, lyophilized, and spray-dried vaccine and pharmaceutical products at preclinical and pilot scale and conduct assays to discern the impact of formulation and packaging changes and temperature exposures on vaccines.

## **1. Leadership and organizational capability**

Darin Zehrung, MBA, will serve as the primary investigator and project manager. Mr. Zehrung is a Senior Technical Officer with the PATH Technology Solutions Program and serves as portfolio leader for the VPDT portfolio. Mr. Zehrung directs multiple medical device and vaccine packaging and delivery technology projects. He has extensive product-development experience, including overseeing design and engineering activities, human factors evaluations, clinical trials, regulatory strategy development, and cost-effectiveness and business analytical modeling. He is a globally recognized expert in delivery and packaging technologies, whose advice and input has



been sought and accessed by both the public and private sectors. He is also a long-standing member of the PATH's research ethics committee, serving as the medical device expert on the committee and now currently serving as interim co-chair. Mr. Zehrung has a Bachelor of Science degree in human biology and a Master of Business administration degree from Western Washington University.

## **2. Staff capacity**

Mr. Zehrung will draw upon many years of project management experience to plan for the project and lead the team in project implementation and evaluation. He will employ a project management approach to establishing a project charter, a responsibility accountability matrix and work breakdown structure along with specific assignments. Project risks will be identified and managed during the course of project implementation. Fortnightly meetings will occur to ensure adherence to the project timeline, with team members reporting on progress against assigned tasks and other project responsibilities. In addition, Mr. Zehrung will lead regulatory learning activities drawing up existing knowledge and experience in this topic area. He currently resides in the United States.

Savitha Swaminathan, MBA, MS, is a commercialization expert, focused on market assessment, product development, strategic planning, and business analytics in the pharmaceutical, biotechnology, and medical device industries. Ms. Swaminathan will serve as the project's market and commercialization lead implementer. Based in PATH's Seattle office, she works as a commercialization associate under the VPDT portfolio to help identify key stakeholders, develop market-introduction strategies, and integrate varied regulatory, clinical, and manufacturing perspectives into team commercialization activities. She has extensive research experience in virology and immunology and holds Bachelor of Science and Master of Science degrees, both in microbiology, as well as a Master of Business Administration degree from the University of Washington. She currently resides in the United States.

Sarah McGray, MPH, is a program officer in PATH's Technology Solutions Program in the Seattle office, where she manages field research and clinical studies and conducts operational research to inform medical device development. For this project, Ms. McGray will serve as the public health expert. She has explored the impact of injection safety policy on national health systems and has developed user needs assessments and training materials to inform technology design and introduction in low-resource health delivery programs. She holds a Master of Public Health degree from the University of Washington and a Bachelor of Arts degree from Boston University. She currently resides in the United States.

For this project, PATH plans to work with representatives from ministries of health, regulatory authorities, vaccine manufacturers, and packaging and delivery technology manufacturers to obtain the necessary project inputs and information to inform planned analysis activities. Global-level representatives from a variety of organizations such as WHO, UNICEF, GAVI, etc., will be engaged to also inform project learning and analysis. All individuals with whom the project team will interface to meet project objectives and activities will represent seasoned, knowledgeable, and recognized experts at the global or country level.

## Section H. References

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Pfizer Adult Immunization: Illustrative Detailed Implementation Plan	Year One												Year Two												Deliverables
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	
<b>Specific Activities</b>																									
<b>Activity Implementation</b>																									
<b>Objective 1. Determine current state of the market for adult immunizations and assess stakeholder requirements (six countries).</b>																									
Activity 1. Define public health and programmatic priorities in six countries.																									
Activity 2. Landscape of commercially available and pipeline vaccines for adults.																									
Activity 3. Describe market requirements for selected vaccines.																									
<b>Deliverable:</b> Report on adult vaccine market requirements.																									
<b>Objective 2. Characterize adult immunization delivery scenarios, with a focus on maternal immunization, and identify constraints to increased coverage (two countries).</b>																									
Activity 4. Describe programmatic constructs, constraints, and barriers for maternal and other adult vaccination in two countries.																									
Activity 5. Describe regulatory environment for new and existing vaccines and delivery technologies.																									
Activity 6. Describe provider needs and patient preferences.																									
<b>Deliverable:</b> Report of delivery scenarios and barriers to adult vaccination in two countries.																									
<b>Objective 3. Map selected barriers to possible technology solutions.</b>																									
Activity 7. Map packaging and delivery technologies to address requirements and constraints.																									
<b>Deliverable:</b> Final report with matrix of adult vaccines, barriers, and possible technology solutions.																									

## Appendix 1. Logic framework

### Using novel packaging and delivery technologies to improve access to adult vaccines in low-resource settings

	Description	Indicators	Source of Verification	Assumptions
Goal	To improve the health of adults in low- and middle-income countries (LMICs) through increased access to adult, and particularly maternal, vaccines by identifying packaging and delivery options that address market requirements, program priorities, and patient and provider needs.	Disseminate recommendations on packaging and delivery options to increase coverage to priority adult vaccines.		This project will not be doing health impact evaluation.
Objectives	Determine the current state of the market and program priorities for adult immunizations in LMICs. (Six countries)	<p>Prioritization of adult vaccines for public health programs in six LMICs.</p> <p>Market requirements identified for priority vaccines in six countries.</p>	<p>Structured interviews with key country immunization stakeholders in six countries.</p> <p>Rapid assessment of priority vaccine attributes and market requirements.</p>	Country stakeholders will be concerned and sufficiently informed about adult vaccines to be able to prioritize.

	Description	Indicators	Source of Verification	Assumptions
	<p>Characterize adult immunization delivery scenarios, with a focus on maternal immunization, and identify constraints to increased coverage (two countries).</p>	<p>Adult immunization-delivery scenarios defined.</p> <p>Barriers to achieving coverage with adult vaccines identified.</p>	<p>Country vaccination data.</p> <p>Published or unpublished reports.</p> <p>Interviews with key stakeholders.</p>	<p>Sufficient knowledge available in target countries regarding adult vaccination.</p>
	<p>Map packaging and delivery technologies (available or in development) to address requirements and barriers identified under Objectives 1 and 2.</p>	<p>Key barriers to adult vaccination identified.</p> <p>List of vaccine packaging/delivery technology options.</p> <p>Matrix of vaccines, barriers, and possible technology solutions.</p>	<p>Reports from Objectives 1 and 2.</p> <p>Review by key stakeholders.</p>	<p>Select barriers will be best addressed through technology innovations (vs. program innovations).</p>

	Description	Indicators	Source of Verification	Assumptions
Outcomes	<p>Evidence of program priorities, barriers to coverage, and opportunities for increasing access to adult vaccination.</p> <p>Increased awareness of barriers and opportunities to increase coverage of adult vaccination.</p>	<p>Reports disseminated in professional forums and on relevant websites.</p>	<p>Report on market requirements, program priorities, and priority vaccine attributes.</p> <p>Report on delivery scenarios and barriers to coverage.</p> <p>Matrix of vaccines, barriers, and possible technology solutions.</p>	<p>Evidence of priorities, barriers, and opportunities for adult vaccination will lead to increased uptake of vaccines.</p> <p>New vaccines in the pipeline will not displace priority for currently available vaccines.</p> <p>Vaccine manufacturers will consider factors influencing uptake of adult vaccines in designing delivery methods.</p>

	Description	Indicators	Source of Verification	Assumptions
Activities	Define public health and programmatic priorities.	List of program priorities for vaccines.	Literature reviews/desk research.	Stakeholders will be willing to discuss adult vaccines.
	Conduct landscape of commercially available and pipeline vaccines for adults.	Landscape of available and pipeline vaccines.	In-depth interviews. Email questionnaires.	Literature is available on adult vaccines in LMICs.
	Describe market requirements for selected vaccines.	Report on markets for adult vaccines (public and private sectors).	Stakeholder surveys. Online surveys.	Vaccine manufacturers will share market information.
	Describe programmatic constructs, constraints, and barriers for maternal and other adult vaccination in two countries.	Descriptions of programmatic approaches to delivery (settings, advocacy, behavior change communication [BCC], training, incentives, etc.).	Phone interviews. Contextual inquiry/ethnographic observation. Mapping exercise.	Country research reviews will not cause delays.
	Describe regulatory environment for new and existing vaccines and delivery technologies.	Report on regulatory environment for new vaccines.		
	Describe provider needs and patient preferences.	Report on provider and patient needs/priorities.		
	Map barriers to coverage to appropriate packaging and delivery technology options.	Matrix of constraints to coverage and packaging and delivery technologies.		





September 29, 2014

Britta Lassmann, MD  
Program Director  
International Society for Infectious Diseases  
9 Babcock St.  
Brookline, MA 02446

**Re: Grant ID 16217821 — Using novel packaging and delivery technologies to improve access to adult vaccines in low-resource settings**

Dear Dr. Lassmann,

This letter confirms PATH's commitment to the work outlined in our proposal entitled *Using novel packaging and delivery technologies to improve access to adult vaccines in low-resource settings*.

PATH is an international nonprofit organization that creates sustainable, culturally relevant solutions, enabling communities worldwide to break longstanding cycles of poor health. With offices in 21 countries, PATH works in more than 70 countries in the areas of health technologies, maternal and child health, reproductive health, vaccines and immunization, and emerging and epidemic diseases.

Drawing upon years of experience in development of vaccine products and delivery technologies, PATH will conduct an assessment of low- and middle-income country adult immunization-delivery scenarios, including market requirements, program priorities, and user needs. We will identify possible constraints that may limit coverage of existing and future adult vaccines and map selected constraints to innovative packaging and delivery technologies that may help to optimize adult vaccine coverage.

PATH looks forward to working on this exciting project.

Sincerely,

Steve Davis  
Chief Executive Officer