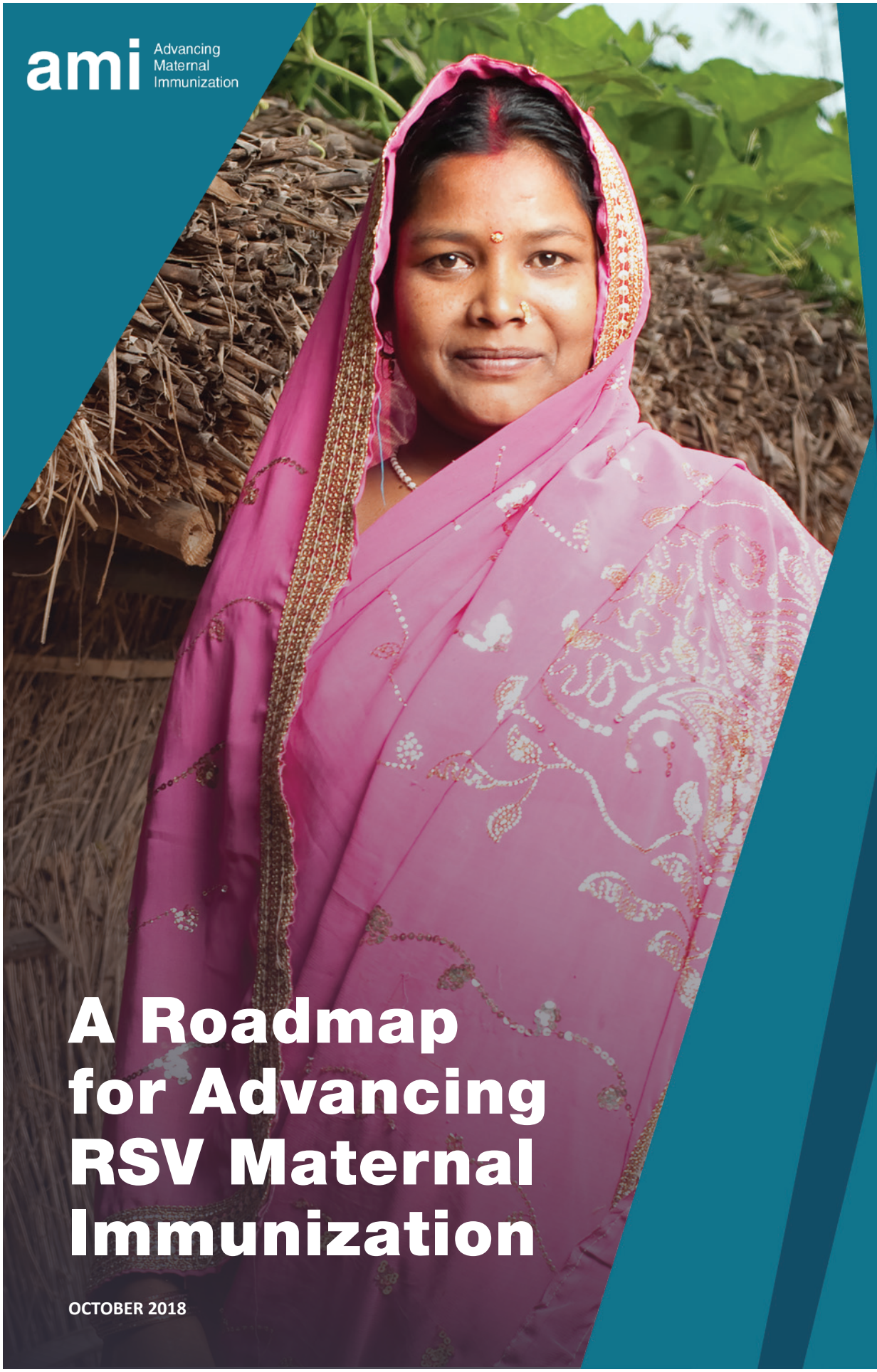
ami Advancing Maternal Immunization



A Roadmap for Advancing RSV Maternal Immunization

OCTOBER 2018

ACKNOWLEDGEMENTS

This roadmap was created with expert input from over 60 individuals across 25 organizations in 14 countries. The Advancing Maternal Immunization (AMI) secretariat is grateful for the shared wisdom, advice, and feedback that guided the development of this work. We also thank the individuals who contributed to the research, writing, editing, and formatting of this document. Lastly, we thank the Bill & Melinda Gates Foundation for supporting this work.

ABOUT AMI

The AMI collaboration brings together diverse stakeholders from around the world and across immunization and maternal, newborn, and child health programs to identify a pathway to enable informed decision-making and introduction of maternal RSV vaccines, particularly in LMICs, and to provide tools to help researchers, decision-makers, implementers, and others navigate that pathway successfully. AMI's current focus is on maternal immunization against an important cause of infant death and illness—respiratory syncytial virus (RSV). Maternal vaccines are being developed for RSV and could be available in a few years, underscoring a need to establish an environment poised for vaccine decision-making and introduction now. AMI is working toward this end by developing a gap analysis and roadmap to facilitate informed global, regional, and country decisions around maternal RSV vaccines, and to identify a strategy for meeting introduction and uptake requirements in LMICs.

This roadmap is based on research funded by the Gates Foundation. The findings and conclusions contained within are those of the authors and do not necessarily reflect positions or policies of the Gates Foundation.

This roadmap was developed in collaboration with the World Health Organization (WHO). The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of WHO.

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LIST OF ABBREVIATIONS

A&C	Advocacy and communications
AEFI	Adverse events following immunization
AMI	Advancing Maternal Immunization collaboration
ANC	Antenatal care
EPI	Expanded Programme on Immunization
GAIA	Global Alignment of Immunization safety Assessment in pregnancy
HDSS	Health and demographic surveillance systems
IMPRINT	Immunising Pregnant Women and Infants Network
LIC	Low-income country
LMIC	Low- and middle-income country
mAb	Monoclonal antibody
MI	Maternal immunization
MIACSA	Maternal Immunization and Antenatal Care Situation Analysis
MNCAH	Maternal, newborn, child, and adolescent health
MNCH	Maternal, newborn, and child health
MNT	Maternal and neonatal tetanus
PQ	Prequalification
RITAG	Regional Immunization Technical Advisory Groups
RSV	Respiratory syncytial virus
RSV MI	Respiratory syncytial virus maternal immunization
SAGE	World Health Organization's Strategic Advisory Group of Experts
STAGE	World Health Organization's Strategic and Technical Advisory Group on MNCAH
VIS	Vaccine Investment Strategy
WHO	World Health Organization

PATH/Felix Masi

EXECUTIVE SUMMARY

PATH/Andrew Berends

Developed by the Advancing Maternal Immunization (AMI) collaboration, this roadmap outlines priority next steps for advancing maternal immunization (MI) against an important cause of acute lower-respiratory illness in infants—respiratory syncytial virus (RSV). This resource distills actions to generate the evidence and conditions needed by global and country decision-makers, public health program planners, and implementers to introduce and optimize RSV MI in low- and middle-income countries (LMICs). While this roadmap provides a broad view of what is needed to make the introduction and wide-scale use of RSV MI in LMICs possible, it also recognizes that progress depends on many factors not yet guaranteed, including the generation of remaining evidence required for decision-making; supportive global and country decisions to recommend and prioritize the vaccine; and health systems and services prepared to deliver the vaccine routinely, efficiently, and equitably. This roadmap highlights activities that address critical gaps in essential evidence and conditions previously identified through AMI's July 2018 *Advancing RSV Maternal Immunization: A Gap Analysis Report.*[1] Activities identified as most urgently needing action are termed 'near-term activities' and span the following areas of work:

Ensuring the availability of safe, effective, and affordable maternal RSV vaccines—Work in this area calls for technical assistance to manufacturers to make sure that RSV vaccines meet performance, supply, and delivery needs for LMICs and to support LMICs in ensuring that systems are in place to track the safety and impact of maternal immunization.

Enabling evidence-based global and country decision-making around maternal RSV vaccines—This work includes increasing stakeholder awareness of the burden of RSV disease and the public health case for the vaccine and ensuring informed policy and financing decisions around its introduction in LMICs.

Enabling systems and services to routinely, efficiently, and equitably deliver maternal RSV vaccines—Through formative research and demonstration projects, activities in this area support coordination between immunization and maternal, newborn, and child health (MNCH) programs to ensure that operations and logistics are in place to optimally deliver the vaccine, health care personnel are empowered to provide it to pregnant women, and systems are prepared to monitor its implementation and resulting outcomes.

This roadmap also briefly describes mid- to long-term activities that address critical gaps, but either have more flexible timelines, require specific milestones to be achieved before work on them can begin, or build on results from earlier activities. AMI will update this roadmap annually as work progresses and new gaps are identified.

BACKGROUND

While vaccines are one of the most powerful disease prevention tools in global health, achieving protection via active immunization often requires multiple doses given over time, leaving infants susceptible to some life-threatening diseases that occur in the first months of life. An approach to addressing this challenge is to immunize mothers during pregnancy, or MI, which provides immunity that they then pass to their infants, conferring protection at birth and for months thereafter. Despite a safe and effective track record against several diseases including maternal and neonatal tetanus (MNT), influenza, and pertussis, MI's full potential has yet to be tapped and its availability in LMICs beyond MNT prevention is limited.

Opportunities for advancing MI are on the horizon, particularly against RSV. A cause of mostly mild illness in older children and adults, RSV can lead to serious complications like pneumonia and bronchiolitis in infants and may also lead to long-term health problems like asthma.[2,3] Every year, it hospitalizes 1.4 million infants less than six months old and sickens more than 30 million children under five years of age worldwide, killing more than 120,000 of them.[4] Almost half of childhood RSV mortality occurs in infants under six months of age and 99% of deaths occur in resource-limited countries.[4]

Supportive therapy for cases of severe RSV disease is generally inaccessible for a large proportion of families in most LMIC settings. No vaccine is yet approved for RSV prevention and the only monoclonal antibody (mAb) approved for prevention of serious RSV disease is not feasible to provide in LMICs. In recent years, however, multiple RSV vaccine candidates have entered clinical development, the most advanced of which is being developed by Novavax, Inc. and could be approved for a MI indication by 2021. Besides being the first RSV vaccine, it would be the first vaccine specifically licensed with an indication for administration to pregnant women to protect their infants and one of the first vaccines targeted for near simultaneous introduction in high-, middle-, and low-income settings. Gavi, the Vaccine Alliance, the largest funder of vaccines in LMICs, is currently considering offering support for maternal RSV vaccine as part of its 2021–2025 vaccine investment strategy (VIS).

AMI is a collaboration of more than 60 diverse experts from immunization and MNCH sectors. PATH and the World Health Organization (WHO) coordinate AMI, which supports global, regional, national, and sub-national decision-making around RSV MI introduction and uptake. An analysis previously conducted by AMI identified and prioritized the evidence gaps that activities in this roadmap address in its July 2018 *Advancing RSV Maternal Immunization: A Gap Analysis Report*.[1] Evidence needs, if not met, are likely to delay or preclude RSV MI introduction and use in LMICs, driving the urgency for many of the activities described in this roadmap.

Overall, maternal RSV vaccines and their delivery to pregnant women provide opportunities and challenges beyond those associated with traditional infant immunization, especially since implementation is expected to require strong collaboration between immunization and MNCH programs. Work proposed here may have far-reaching effects since advancing readiness for the introduction of RSV MI may benefit alternative RSV countermeasures for young infants such as long-acting RSV mAbs and pave the way for future MI vaccine introductions to reduce the risk of neonatal sepsis. It may also contribute to strengthening antenatal care (ANC) services in general, increase the uptake of other maternal or infant health interventions, and inform a broader MI platform. This roadmap focuses on activities that must start as soon as possible to inform global and country decisions about introducing maternal RSV vaccines in LMICs and effectively deliver them once available. It highlights work underway and identifies existing evidence, experience, and systems that provide valuable foundations to the work proposed—including in ANC, MI, and pneumonia prevention. Furthermore, this RSV MI roadmap builds upon and complements existing guidance documents and takes a broad view of activities needed across the full vaccine development and delivery continuum.[a]

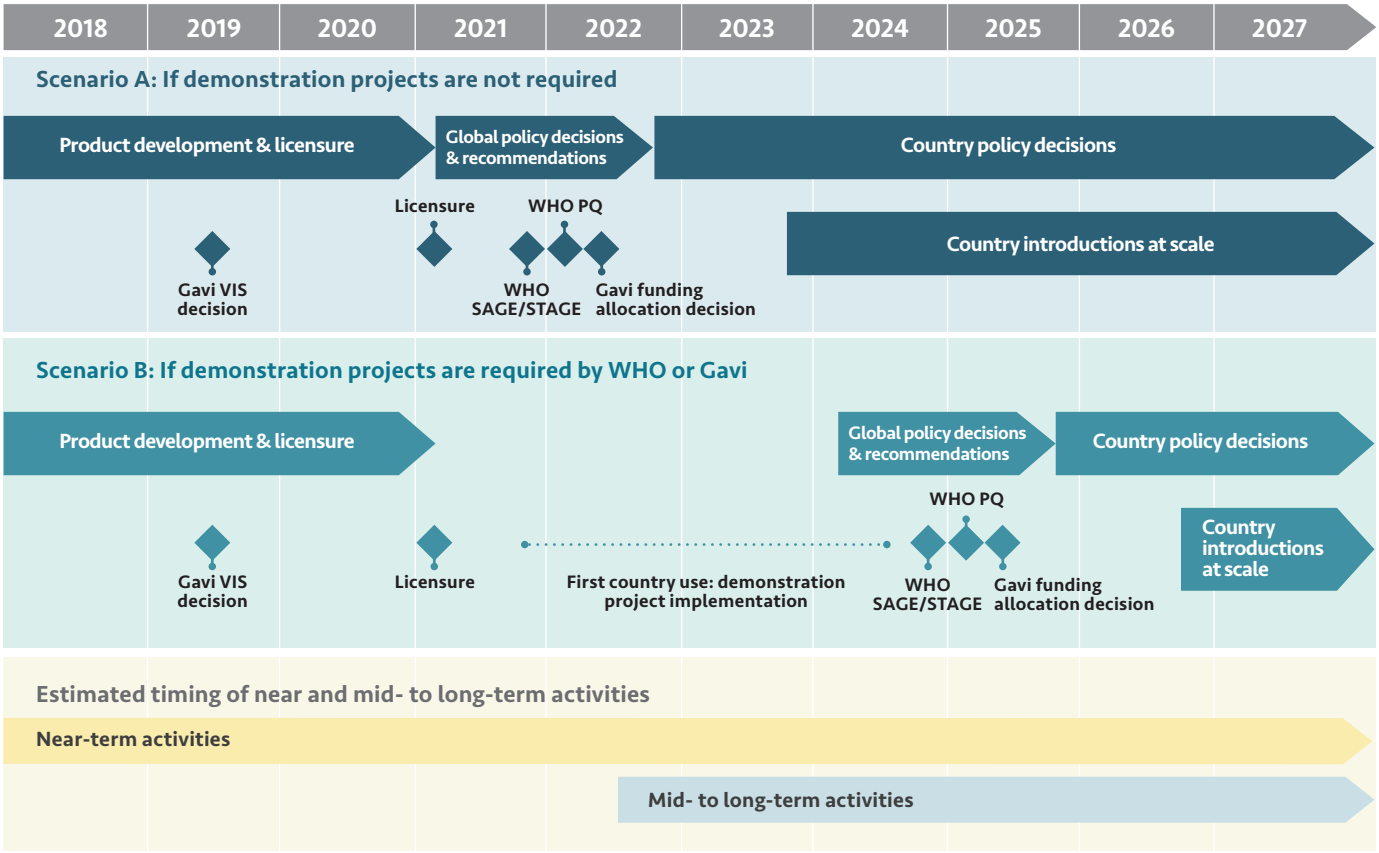
[a]Existing guidance documents include, but are not limited to, WHO's 2017 RSV Vaccine Research and Development Technology Roadmap and Maternal Immunization Safety Monitoring in Low- and Middle-Income Countries: A Roadmap for Program Development by the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS).[5,6]

APPROACH

This roadmap describes activities needed to fill priority gaps identified through AMI's RSV MI gap analysis and a separate survey of over 70 AMI members and other technical experts to confirm priorities. We focus on activities specifically identified as critical for generating required evidence and achieving necessary conditions for advancing RSV MI in LMICs. We divide each activity into sub-activities to provide specificity and clarity around the tasks required to complete it. The roadmap places the over-arching activities on a projected timeline across the vaccine development, policy making, and country introduction continuum, classifying them as either 'near-term' or 'mid- to long-term'. Activities are identified as 'near-term' if planning or implementation of at least one of its sub-activities need to start before early-2022, when the first maternal RSV vaccine is expected to undergo reviews by WHO's Strategic Advisory Group of Experts (SAGE) on Immunization and its newly created counterpart for maternal, newborn, child, and adolescent health (MNCAH), the Strategic and Technical Advisory Group of Experts (STAGE) on MNCAH as well as to be considered for WHO prequalification (PQ). Activities with sub-activities in which planning or implementation are not needed until mid-2022 and onwards are referred to as 'mid- to long-term.' The dates of key milestones on the timeline are based on current understanding, are approximate, and will be updated as additional information becomes available.

In Figure 1, key milestones contextualize the urgency of the activities outlined in this roadmap. Given previous experience with vaccine introduction and the potential request by SAGE for information on vaccine delivery feasibility in low-income contexts before fully endorsing a new vaccine, we present two distinct timelines and scenarios. Scenario A describes global decision-making directly after vaccine licensure and Scenario B includes the conduct of demonstration projects to evaluate implementation feasibility before global decision-making, which extends the estimated timing of both country decision-making and vaccine use at scale by three years.

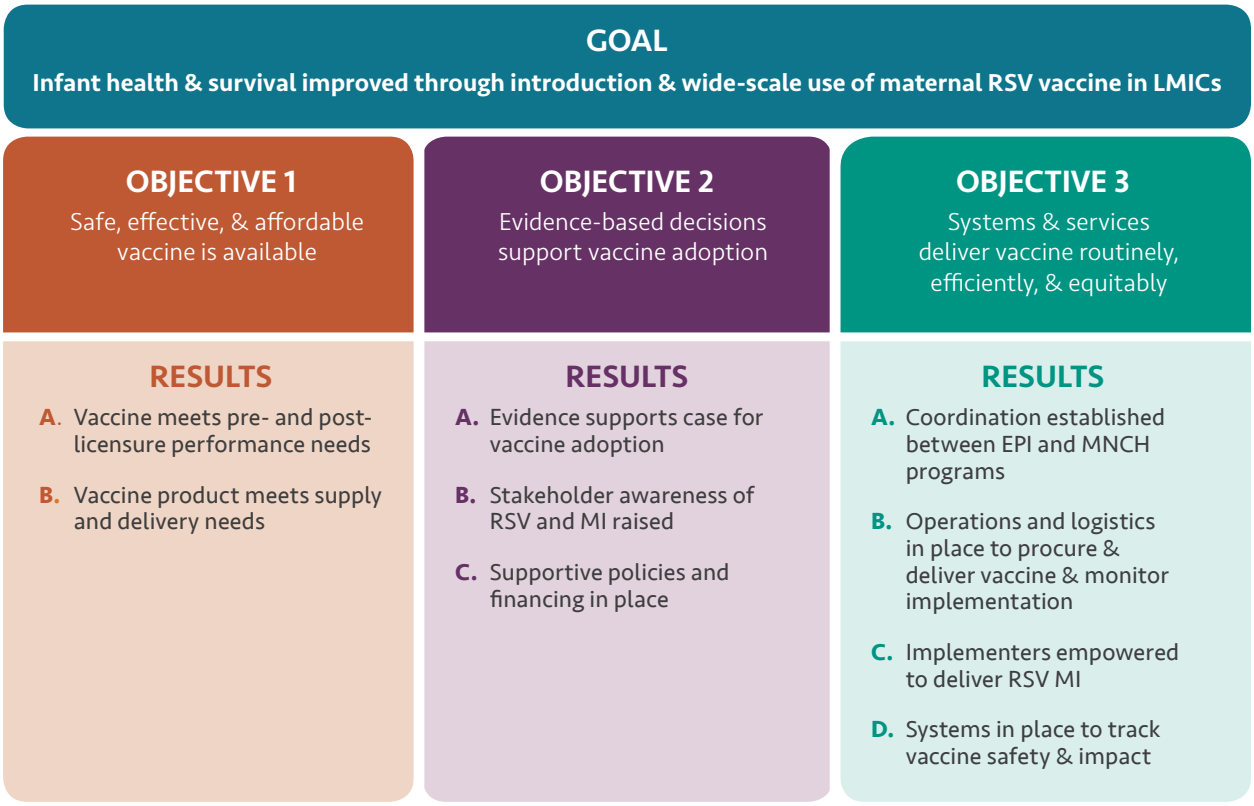
FIGURE 1. **Maternal RSV vaccine development and introduction continuum, key milestones, and recommended timing of planning or implementation of activities, by scenario.**



VIS-Vaccine Investment Strategy

Overall, we consider the goal of advancing RSV MI to be improved infant health and survival in LMICs. In Figure 2, we map the objectives and results that must be achieved to reach this goal, but do so in recognition that not all factors along the way are guaranteed, namely the generation of remaining evidence required for decision-making; supportive global and country decisions to recommend and prioritize the vaccine; and health systems and services prepared to deliver the maternal vaccine routinely, efficiently, and equitably. We also describe how near-term and mid- to long-term activities connect to interim results that, if successful, will lead to achieving the objectives needed to reach the goal (see Figures 3 and 4).

FIGURE 2. **Activity objectives and results leading to the goal of improved infant health and survival in LMICs through RSV MI**



PRIORITY ACTIVITIES / NEAR-TERM

PATH/Evelyn Hockstein

While a variety of evidence and work are required for routine RSV MI in LMICs to become feasible, the activities and sub-activities highlighted in this section require action by early-2022, when the first maternal RSV vaccine is expected to undergo SAGE and possibly STAGE review and be considered for PQ. These near-term activities are characterized as urgent due to: 1) an imminent decision point; 2) the length of time needed to plan and accomplish the activity; 3) the reliance of other key activities on the results or outcomes of the activity; and/or 4) the need for continuity with ongoing or recent activities.

In Figure 3, we map how the results of near-term activities identified in subsequent sections of this roadmap connect with objectives that need to be achieved to advance RSV MI decision-making, introduction, and wide-scale use in LMICs. We also show how these connections contribute to the goal of improving infant health and survival when essential gaps are filled and objectives are met.

FIGURE 3. **Connections between near-term activities, results, and objectives that need to be achieved to enable RSV MI decision-making and wide-scale use in LMICs to improve infant health and survival.**

GOAL
Infant health & survival improved through introduction & wide-scale use of maternal RSV vaccine in LMICs

	OBJECTIVE 1: Safe, effective, & affordable vaccine is available		OBJECTIVE 2: Evidence-based decisions support vaccine adoption			OBJECTIVE 3: Systems & services deliver vaccine routinely, efficiently, & equitably			
ACTIVITY	**RESULT A** Vaccine meets pre- & post-licensure performance needs	**RESULT B** Vaccine product meets supply & delivery needs	**RESULT A** Evidence supports case for vaccine adoption	**RESULT B** Stakeholder awareness of RSV & MI raised	**RESULT C** Supportive policies & financing in place	**RESULT A** Coordination established between EPI & MNCH programs	**RESULT B** Operations & logistics in place to procure & deliver vaccine & monitor implementation	**RESULT C** Implementers empowered to deliver RSV MI	**RESULT D** Systems in place to track vaccine safety & impact
1. Enhance RSV surveillance in LMICs			●						●
2. Evaluate vaccine performance against severe infant RSV disease	●								
3. Assess RSV prevention effects on wheezing & reactive airway disease			●						
4. Assist vaccine manufactures to meet LMIC decision & implementation requirements		●							
5. Establish background obstetric & infant outcome rates & monitor vaccine safety	●								●
6. Convene a RSV vaccine market working group		●			●				
7. Conduct vaccine impact & cost-effectiveness modelling			●		●	●	●		
8. Evaluate vaccine delivery costs & financing needs			●		●				
9. Conduct formative research in LMICs			●	●	●	●	●	●	
10. Assess A&C needs & develop strategies				●	●			●	
11. Conduct demonstration projects	●	●	●	●	●	●	●	●	●

For each activity described below, we indicate the objective(s) and result(s) to which the work will contribute, as illustrated in Figure 3. We further break down the activities into sub-activities and estimate the year that planning or implementation needs to start. We indicate the primary milestones that the evidence will inform, including **SAGE** (and possibly STAGE) recommendations, WHO **PQ**, **Gavi** financing decisions, and **LMIC** licensure, decision-making, and/or implementation. Assumptions and an illustrative list of relevant ongoing work are also included. For a more detailed overview of existing relevant work and forthcoming evidence, see the RSV MI gap analysis.[1]

1. Enhance global RSV surveillance capacity in sentinel sites in LMICs to quantify disease burden and seasonality

OBJECTIVES: 2 A 3 D

Available information indicates that RSV causes significant disease burden globally.[4] Though relevant data are available from some low-income contexts, additional data are needed from LMIC hospital and non-hospital settings that characterize outcomes by narrow age bands, stratify by co-morbidities, and can be harmonized across studies.[7] Specifically, the burden of disease must be better characterized in communities lacking access to adequate care for severe disease given that data from a recent study suggest that RSV may be a leading contributor to mortality in children under five years of age, including infants.[8] Finally, data must be presented in appropriate formats to support both global and country decision-making.

This activity will respond to countries or regions that want contextually relevant data regarding levels of morbidity/mortality and age-incidence of serious disease to justify a maternal RSV vaccine's local relevance. It also provides a baseline for measuring post-introduction vaccine impact and for effectiveness studies using a case-control design in the period directly after introduction. We consider this activity near term because the length of time required to collect data must span several years and seasons to provide sufficient information for meaningful interpretation.

Sub-activities, estimated start year, and key milestones supported

2019	• Conduct reviews of published and grey literature on RSV disease burden originating from LMIC sentinel sites; use meta-analyses to identify regional gaps that require additional studies; and synthesize existing information on narrowly stratified risk factors and outcomes.	**SAGE LMIC**
	• Develop a routine RSV disease surveillance and vaccine impact assessment strategy.	**SAGE LMIC**
	• Establish population-based surveillance in select LMIC sites to estimate RSV disease incidence, including community-based burden.	**SAGE LMIC**
2020	• Establish representative regional surveillance networks to gather data on RSV seasonality.	**SAGE LMIC**

Assumptions

- WHO serves a convening, strategic, and coordinating role for surveillance and vaccine impact assessments.
- The Novavax Phase 3 trial provides age-stratified disease data, but data are insufficient from low-income countries (LICs) and populations with relevant co-morbidities (e.g., HIV, prematurity, low birth weight, and indoor air pollution exposure).[b]
- Surveillance includes standardized definitions and data collection to enable cross-study/site comparisons.
- Data from another country will be sufficient for some country decision-makers.
- Strategies and tools for monitoring and linking pneumonia disease surveillance and vaccine impact studies through the International Vaccine Access Center's VIEW-hub will be applicable to RSV.[9]

[b]The maternal RSV vaccine candidate currently furthest along in development is Novavax, Inc.'s RSV F vaccine candidate. A Phase 3 clinical trial of the candidate vaccine is in progress in seven high-income countries (i.e., United States, United Kingdom, Spain, Chile, Argentina, Australia, and New Zealand) and four middle-income countries (i.e., Bangladesh, Mexico, Philippines, and South Africa). Final efficacy and safety results are expected in Q1 and Q3 2019, respectively.

Current work in progress

- RSV-specific findings from the Pneumonia Etiology Research for Child Health–PERCH study which are expected to be published in 2019.
- WHO's RSV Surveillance Pilot is developing a global strategy and roadmap for RSV surveillance.[c]
- Ongoing RSV surveillance (including, but not limited to, sites in Kenya, South Africa, and The Gambia).[d]
- Novavax Phase 3 trial.
- Results from a GlaxoSmithKline RSV disease burden study in nine countries (no LICs) following children under six years of age.
- Gates Foundation-funded studies to evaluate community mortality of children in Argentina, Zambia, India, and Pakistan (interim results published for Argentina).[8,e]

2. Evaluate maternal RSV vaccine safety, immunogenicity, and effectiveness against severe RSV disease in infants to inform applicability for use in LMIC contexts

OBJECTIVE: 1 A

This activity will generate essential data about the maternal RSV vaccine's performance and optimal use beyond what clinical trials will generate for first licensure. Planning for gathering this additional data should start immediately and include consultation with policy makers to align with their likely information needs. Doing so will enable the appropriate study(ies) to be efficiently initiated once supportive vaccine safety and efficacy data are available. Coordinating vaccine performance data generation with other efforts to gather information for WHO decision-making (such as demonstration projects outlined in near-term activity 11) will be important to leverage resources and share evolving data.

Sub-activities, estimated start year, and key milestones supported

2019	• Conduct vaccine safety and effectiveness studies in co-morbid populations excluded from the Novavax Phase 3 trial (e.g., HIV+, malaria+, women with prior adverse pregnancy outcomes, and preterm infants).	**SAGE LMIC**
	• Conduct studies to assess vaccine safety and immunogenicity when co-administered with tetanus-containing vaccine and/or given across multiple pregnancies.	**SAGE LMIC**
	• Conduct studies to evaluate the potential for broadening the RSV maternal vaccination window, particularly for regions where assessing gestational age is challenging and where ANC coverage during the second and third pregnancy trimesters is low.	**SAGE LMIC**

Assumptions

- WHO's "Guidelines on clinical evaluation of vaccines; regulatory expectations" inform maternal RSV vaccine clinical development requirements.[10]
- Clinical criteria developed by WHO for RSV case definitions are used in vaccine efficacy trials.[7]
- Clinical trials provide vaccine safety data (including infant follow up for enhanced respiratory disease); efficacy; and duration of protection in populations across multiple WHO regions.
- Once established, a RSV SAGE working group reviews available vaccine efficacy and safety data and identifies remaining information that SAGE may require before WHO makes a recommendation on vaccine use.

[c]WHO's RSV Surveillance Pilot collects RSV disease burden, seasonality, and risk factor data in 14 countries using the Global Influenza Surveillance and Response System network. Results are expected in 2019. [d]Site sponsors include James Nokes (Kenya), Shabir Madhi (South Africa), and Beate Kampmann (The Gambia). [e]Study sponsors include Fundación INFANT (Argentina), Boston University (Zambia), Emory University (Pakistan), and University of Colorado, Denver (India).

- Safety and effectiveness data gathered in high- or middle-income settings with high-quality monitoring infrastructures may contribute to decision-making in LMICs; however, data may lack generalizability given contextual differences.
- Studies on vaccine co-administration safety and immunogenicity and the need for dosing across multiple pregnancies can be conducted in non-pregnant women.

Current work in progress

- Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) case definitions are being piloted to assess their ability to measure obstetric and neonatal health outcomes.[15]
- Novavax Phase 3 trial.
- WHO Technologies, Standards, and Norms is drafting "Guidelines on the quality, safety, and efficacy of RSV vaccines," targeting approval by the Expert Committee on Biological Standardization in 2019.

3. Assess effects of RSV disease prevention in infancy on recurrent wheezing and reactive airway disease

OBJECTIVE: 2 A

Although not essential to establishing the primary outcomes of vaccine safety and efficacy for vaccine licensure, evidence of RSV prevention's effect on life-long health could support decision-making and priority setting around maternal RSV vaccine at both global and country levels by expanding our understanding of the full public health benefit of the intervention. This activity informs maternal RSV vaccine's impact on recurrent wheeze and asthma in children of vaccinated mothers. Planning needs to start immediately to retain subjects from the Novavax Phase 3 trial and subsequent large-scale RSV intervention trials.

Sub-activities, estimated start year, and key milestones supported

2019	• Conduct long-term follow-up evaluations among infants born to maternal RSV vaccine clinical trial cohorts to assess the effect of RSV prevention in infancy on recurrent wheeze (young children) and asthma (school-aged children).	**SAGE LMIC**

Assumptions

- Continuous and long-term follow up of clinical trial participants occurs.
- Diagnosing recurrent reactive airway disease episodes and confirmed asthma in LMICs is possible to measure attributable risks.

Current work in progress

- WHO is developing "Methodological considerations for studies to measure the association between RSV LRTI and wheeze/asthma," for which a consultation meeting is expected in early 2019.

4. Provide technical assistance to manufacturers to ensure vaccines meet LMIC decision-making and implementation requirements

OBJECTIVE: 1 B

Achieving first licensure for a vaccine is a significant milestone, but many decision-making processes must occur before the vaccine can have impact in LMICs. Country access to vaccines can be accelerated by providing technical assistance to ensure that the manufacturer communicates with global stakeholders early and meets their requirements, and evidence is available that demonstrates the vaccine's appropriateness for LMIC use.

Sub-activities, estimated start year, and key milestones supported

2019	• Provide technical assistance to manufacturers to ensure that the vaccine clinical data package is complete and appropriately communicated to inform SAGE and STAGE recommendations.	**SAGE**
	• Provide technical assistance to ensure that manufacturers meet quality and programmatic suitability requirements and/or preferences for vaccine use in LMICs.	**SAGE, PQ Gavi, LMIC**
	• Provide technical assistance to manufacturers to ensure that vaccine-specific information is appropriately communicated and available for country decision-making.	**LMIC**

Assumptions

- Vaccine manufacturers may not have experience with global policy and PQ processes, including WHO's Programmatic Suitability for Prequalification criteria and LMIC market access.

Current work in progress

- PATH is exploring blow-fill-seal vaccine delivery devices to increase programmatic suitability and reduce cost and cold chain footprint.

5. Establish background rates of adverse obstetric and infant outcomes and establish or strengthen systems to monitor vaccine safety signals

OBJECTIVES: 1 A 3 D

Successful routine RSV vaccine delivery to pregnant women will require a robust tracking system for adverse pregnancy outcomes and adverse events following immunization (AEFI) monitoring and surveillance, particularly in early-adopting countries. Work under this activity will help establish background rates of adverse obstetric and neonatal outcomes to subsequently evaluate vaccine impact and identify any safety signals. Extended monitoring will also be required in early-adopting sites to demonstrate vaccine safety after exposure to natural RSV infection. This activity will support efforts to create consistent vaccine pharmacovigilance across countries, meet and maintain standards, and provide accurate data on vaccine safety. It also enables global and country stakeholders to coordinate and manage crises (real or perceived) related to the vaccine.

Sub-activities, estimated start year, and key milestones supported

2019	• Conduct a systematic pregnancy surveillance system needs assessment including human resources and data systems.	**SAGE LMIC**
	• Expand existing data sharing and communication/risk management systems between organizations and countries collecting relevant surveillance data to include RSV MI (e.g., US Centers for Disease Control and Prevention, WHO, vaccine manufacturers, etc.).	**SAGE LMIC**
	• Develop training and standardized protocols for AEFI surveillance and investigation.	**SAGE LMIC**
2020	• Establish, leverage, and/or strengthen existing pregnancy surveillance systems to measure rates of adverse obstetric and neonatal outcomes in LMICs.	**SAGE LMIC**
	• Provide technical assistance to countries on adopting recommendations, quality assurance, standardized protocols, and standards of practice for MI pharmacovigilance.	**LMIC**
	• Plan for conducting targeted vaccine safety surveillance studies in countries introducing maternal RSV vaccine.	**SAGE LMIC**

Assumptions

- Existing relevant surveillance programs contribute to MI safety and surveillance initiatives.
- The Global Alliance to Prevent Prematurity and Stillbirth–GAPPS, GAIA, and other existing roadmaps and recommendations are accepted and implemented with consensus.[6,11]
- Linking immunization monitoring to other pregnancy monitoring systems (including stillbirth and birth defect surveillance) is feasible.
- WHO's Global Advisory Committee on Vaccine Safety provides scientific recommendations to WHO, SAGE, and national governments in formulating vaccine safety policies.

Current work in progress

- WHO's Mother and Newborn Information Tracking of Results–MoNITOR.[12]
- A WHO module on reproductive, maternal, neonatal, child, and adolescent health data for routine Health Management Information Systems that includes pregnancy outcomes and MI as core indicators.
- WHO's Maternal and Death Surveillance and Response and perinatal audit.[13]
- Health and Demographic Surveillance Systems (HDSS), including sites from the INDEPTH network (a global network of 48 HDSS sites in 19 countries).[14]
- Ongoing research studies and clinical trials examining MI with other vaccines in LMICs (e.g., vaccine clinical trials through the Immunising Pregnant Women and Infants network [IMPRINT]). IMPRINT is also piloting case definitions for maternal and neonatal adverse events developed under GAIA.[15]
- A map of currently available systems coming out of a September 2018 WHO Birth Defect Surveillance meeting.
- Several large birth defect surveillance initiatives organized by WHO, which may provide useful data.[f, 16-20]

[f]Initiatives include the Newborn and Birth Defects Database in Southeast Asia; the European Surveillance of Congenital Anomalies; the Latin American Collaborative Study of Congenital Malformations; the Vaccines and Medications Surveillance Systems in Pregnancy; and COUNT, the Center for Disease Control's global initiative to reduce death and disability from neural tube defects.

6. Convene a RSV vaccine market working group

OBJECTIVES: 1 B 2 C

A RSV vaccine market working group will provide guidance around fundamental supply and demand issues such as ensuring that initial vaccine demand forecast estimates are aligned with global and country expectations. It will identify the factors important for procuring vaccines for LMICs, anticipate when the vaccine will be available to countries, and help align vaccine demand and supply for LMICs. This activity needs to start directly following a Gavi funding decision and several of the sub-activities listed below can occur as part of a single assessment effort.

Sub-activities, estimated start year, and key milestones supported

2019	• Refine initial demand forecast assumptions and results.	**Gavi, LMIC**
	• Incorporate country perspectives into demand estimates.	**Gavi, LMIC**
	• Assess anticipated vaccine demand relative to supply.	**Gavi, LMIC**
	• Investigate potential factors affecting vaccine price.	**Gavi, LMIC**
	• Provide guidance to manufacturers in planning for international sales, including increasing manufacturing scale in time to meet future demand.	**LMIC**
2020	• Explore alternate vaccine financing and procurement mechanisms for countries ineligible for Gavi support.	**LMIC**

Assumptions

- The lead maternal RSV vaccine candidate is on the path to licensure, and the Gavi Board provisionally supports the vaccine in Gavi's 2018 VIS.

Current work in progress

- WHO Market Information for Access to Vaccines–MI4A project.[g]
- Gavi market-shaping activities using the Healthy Markets Framework.[21]

7. Conduct modelling to examine the effect of alternative delivery strategies on maternal RSV vaccine impact and cost-effectiveness

OBJECTIVES: 2 A 2 C 3 A 3 B

This activity will identify maternal RSV vaccine delivery strategies that have the potential to optimize the vaccine's public health benefit and/or value in different country contexts. Modelling will be important given that RSV occurs seasonally in many settings and the duration of the vaccine's protection is expected to be relatively short—both of which may have implications on the health impact and cost-effectiveness of the vaccine. SAGE and/or STAGE may require the results of this activity to inform their recommendations on preferred vaccine delivery strategies.

Sub-activities, estimated start year, and key milestones supported

2019	• Model alternative strategies that include seasonal or targeted delivery, immunization campaigns, and approaches that strengthen ANC coverage and quality (e.g., location of services, group ANC, and increasing demand for services through behavior change communication or other incentives).	**SAGE Gavi LMIC**

[g]MI4A aims to identify and address vaccine affordability and shortage issues for self-funding and self-procuring countries that are mostly excluded from international support.

Assumptions

- Adequate information is available about RSV's seasonality (and its variability), duration of protection relative to vaccination timing, and the effect of breast-feeding to sustain passive protection in LMICs.

Current work in progress

- University of Edinburgh work supported by WHO to model seasonal mAb and MI feasibility in LMICs (results expected 2019).
- PATH, University of Antwerp, and London School of Hygiene and Tropical Medicine impact and cost-effectiveness models, which could inform delivery strategies.
- WHO Maternal Immunization and Antenatal Care Situation Analysis (MIACSA) (results expected March 2019).[h]

8. Evaluate RSV MI delivery costs and financing needs

OBJECTIVES: 2 A 2 C

This activity will generate needed data on the costs associated with providing MI through ANC. It will also provide cost-of-delivery data to inform cost-effectiveness studies. These data will support priority setting, public health budgeting, and vaccine delivery strategy selection. This information can be gathered in conjunction with the formative research described in near-term activity 9.

Sub-activities, estimated start year, and key milestones supported

2020	• Collect cost-of-delivery data for different delivery strategies and levels of vaccine integration with ANC.	**SAGE Gavi LMIC**
	• Compare delivery costs to existing studies for other vaccines to determine the need for additional data.	**SAGE Gavi LMIC**

Assumptions

- Data on delivery costs are collected as part of formative research.
- Demonstration projects occur, as described in near-term activity 11.

Current work in progress

- WHO's FLUTOOL/SIICT, an influenza-specific costing tool, which is being enhanced and could inform RSV-specific costs.

[h]WHO's MIACSA project uses a mixed methods approach to address overarching questions around service delivery models for tetanus MI in LMICs and their correlation with tetanus MI performance in LMICs, the effect of selected systems factors with tetanus MI performance in LMICs, and the interplay of these systems factors and service delivery models with tetanus MI performance in LMICs. Stakeholder feedback was solicited by surveying MNCAH and EPI stakeholders in more than 100 countries, followed by in-depth assessments in a sub-sample of countries.

9. Conduct formative research to inform optimal vaccine delivery approaches

OBJECTIVES: 2 A, 2 B, 2 C, 3 A, 3 B, 3 C

In addition to data on vaccine safety and efficacy, global and country decision-makers and implementers will likely require evidence around vaccine acceptability and demand to inform their decisions around RSV MI. This research should optimally be conducted in countries likely to be among the first to consider introducing the vaccine and will lay the groundwork for subsequent demonstration projects described in near-term activity 11. As soon as supportive maternal RSV vaccine safety and efficacy data are available, the formative research studies should begin in several representative countries identified by consensus criteria. Sub-activities can be addressed simultaneously under a coordinated effort within each country.

Sub-activities, estimated start year, and key milestones supported

2019	• Gain key stakeholder consensus on criteria for identifying countries to conduct formative research and possible demonstration projects.	**SAGE LMIC**
	• Conduct knowledge, awareness, and perception studies in-country around RSV disease; RSV prevention; MI acceptability; demand for MI and vaccination during ANC delivery; and RSV vaccine's perceived priority level relative to other current and planned vaccine and MNCAH interventions.	**SAGE LMIC**
	• Conduct feasibility studies that evaluate country-level MI drivers and barriers and account for current practices, different delivery channels, and immunization and MNCH program responsibilities from system, provider, community, and beneficiary perspectives.	**SAGE LMIC**

Assumptions

- A task force of key stakeholders is established to provide global guidance and technical assistance for maternal RSV vaccine delivery in LMICs.
- Country RSV vaccine prioritization and demand is part of an established planning process carried out by ministries of health and their national immunization technical advisory groups-NITAGs, with input from key stakeholders that consider new vaccines and disease priorities, current Expanded Programme on Immunization (EPI) performance, funding, and vaccine supply. Key planning documents such as the Comprehensive Multi-Year plan and National Immunization Plans reflect these priorities.

Current work in progress

- MIACSA.
- Monitoring framework development for WHO's new ANC guidelines, "WHO recommendations on ANC for a positive pregnancy experience," which can inform maternal RSV vaccine introduction.
- The Quality of Care Network, which aims to reduce preventable maternal and newborn morbidity and mortality and improve mothers' care experiences—warrants exploration into the possibility of expanding their work to ANC.[22]

10. Assess advocacy and communications (A&C) needs and develop strategies to raise awareness, communicate value, and support informed RSV MI decision-making

OBJECTIVES: 2 B 2 C 3 C

Work proposed under this activity will assess A&C needs for supporting awareness and policy- and decision-making and inform strategy development for meeting those needs. Resulting A&C strategies will need to be calibrated appropriately to account for other vaccine and healthcare priorities; the status of evidence around RSV MI; the stage of decision-making; and other factors. Work will identify key audiences and optimal ways to raise awareness and communicate with them. It will equip global, regional, national, and sub-national champions and advocates with appropriate tools and strategies to communicate effectively about RSV, MI, and RSV prevention measures as appropriate; support informed decision-making; and assist planning for vaccine introduction and scale-up. A&C planning will also account for potential communications crises and opposition factors affecting RSV MI. Appropriate and effective stakeholder engagement needs to happen as soon as supportive Phase 3 vaccine safety and efficacy data are available to lay the foundation for evidence-based decision-making around RSV MI. A&C needs and strategies will require multiple assessments and continual refinement to address different contexts and evolving needs.

Sub-activities, estimated start year, and key milestones supported

2019	• Map key global, regional, and country stakeholders and assess knowledge, awareness, and perceptions around RSV, MI, RSV MI, and vaccine integration with ANC.	**SAGE LMIC**
	• Conduct message testing to assess appropriate framing, messaging, and modes of communication to support informed RSV MI decision-making and introduction planning (needs to occur at various time points depending on context).	**SAGE LMIC**
	• Use information generated to create A&C plans that meet global and country level needs and engage and support key stakeholders to implement them as appropriate.	**SAGE LMIC**
2021	• Prepare country decision-making framework for maternal RSV vaccine introduction.	**LMIC**

Assumptions

- RSV awareness and prioritization is currently low, particularly at the country level.
- A&C strategy development and refinement is a fluid process that necessitates revising strategies as evidence evolves and must be tailored to specific global, regional, national, and sub-national contexts.

Current work in progress

- Ongoing efforts by the Gates Foundation to convene MNCAH and vaccine stakeholders to align on introduction and delivery of maternal vaccines.

11. Conduct demonstration projects to inform global policy decisions and validate vaccine delivery feasibility

OBJECTIVES: 1 A | 1 B | 2 A | 2 B | 2 C | 3 A | 3 B | 3 C | 3 D

This activity and its timing depends on requirements by SAGE, and possibly STAGE, for information on the feasibility of RSV MI delivery before fully endorsing the vaccine for use in LMICs. While some lessons concerning delivery are available based on experience immunizing pregnant women with tetanus toxoid-containing and influenza vaccines as well as delivering routine ANC services, key nuances in maternal RSV vaccines warrant additional work (e.g., low disease awareness, a narrow gestational-age window for vaccination, expected routine delivery through ANC, coordination with EPI for data collection, reporting, and safety monitoring, etc.).[23-25] Demonstration projects in early-introducing countries will validate the formative research described in near-term activity 9 and test the feasibility of different vaccine delivery approaches through the public health system. These projects will be an opportunity for countries to demonstrate that delivering RSV MI is possible and test approaches to optimize its use, and can inform decision-making in other countries. If required for WHO decision-making expected in early 2022, planning for these studies should begin in 2019. Coordinating demonstration projects with other efforts to generate information for WHO decision-making in this timeframe (such as vaccine performance evaluations in near-term activity 2) will be important for leveraging resources and sharing evolving data.

Sub-activities, estimated start year, and key milestones supported

2019	• Hold consultation with SAGE, and possibly STAGE, to identify likely evidence requirements to support policy deliberations.	**SAGE LMIC**
	• Conduct preliminary conversations with country-level stakeholders in potential demonstration country locations.	**LMIC**
	• Develop demonstration project plan in select countries to evaluate feasibility, delivery approaches and requirements, and effective demand generation/communication strategies.	**SAGE LMIC**
2021	• Plan for study to evaluate approaches for optimizing RSV MI coverage.	**SAGE LMIC**
	• Plan for study to assess impact of integrating RSV vaccine with existing ANC services on service quality and uptake and overall EPI coverage.	**SAGE LMIC**

Assumptions

- SAGE and/or STAGE requires evidence of RSV MI acceptability and delivery feasibility before making policy decisions.
- A vaccine safety reporting system is in place in demonstration countries or will be established two years before vaccine introduction.

Current work in progress

- MIACSA.

PRIORITY ACTIVITIES / MID- TO LONG-TERM

PATH/Mike Wang

The activities outlined in this section respond to gaps identified as essential in AMI's RSV MI gap analysis but have timelines that are either more flexible than the near-term activities or depend on achieving milestones or obtaining information from earlier activities. These mid- to long-term priority activities should begin from mid-2022 onwards to meet identified needs toward RSV MI decision-making, introduction, and scale up in LMICs.

In Figure 4, we map how the results of mid- to long-term activities connect with objectives that ideally need to be achieved to advance RSV MI decision-making, introduction, and wide-scale use. We also show how these connections contribute to the goal of improving infant health and survival in LMICs if essential gaps are filled successfully and objectives are attained.

FIGURE 4. **Connections between mid- to long-term activities, results, and objectives that need to be achieved to enable maternal RSV immunization decision-making and wide-scale use in LMICs to improve infant health and survival.**

GOAL
Infant health & survival improved through introduction & wide-scale use of maternal RSV vaccine in LMICs

	OBJECTIVE 1 **Safe, effective, & affordable vaccine is available**		**OBJECTIVE 2** **Evidence-based decisions support vaccine adoption**			**OBJECTIVE 3** **Systems & services deliver vaccine routinely, efficiently, & equitably**			
ACTIVITY	**RESULT A** Vaccine meets pre- & post-licensure performance needs	**RESULT B** Vaccine product meets supply & delivery needs	**RESULT A** Evidence supports case for vaccine adoption	**RESULT B** Stakeholder awareness of RSV & MI raised	**RESULT C** Supportive policies & financing in place	**RESULT A** Coordination established between EPI & MNCH programs	**RESULT B** Operations & logistics in place to procure & deliver vaccine & monitor implementation	**RESULT C** Implementers empowered to deliver RSV MI	**RESULT D** Systems in place to track vaccine safety & impact
1. Evaluate licensed vaccine performance against severe infant RSV disease	●								
2. Provide technical assistance to LMIC decision-makers around introduction & implementation		●	●	●	●		●		
3. Develop a global financing strategy to achieve optimal RSV MI delivery in LMICs			●		●	●			
4. Conduct cost-of-illness studies in underrepresented geographies			●		●				
5. Evaluate vaccine delivery costs & financing needs at the country level			●		●	●	●		

1. Evaluate safety and effectiveness of licensed maternal RSV vaccine against severe RSV disease in infants in relevant contexts

OBJECTIVE: 1 A

- Assess the safety and effectiveness of the maternal RSV vaccine in post-licensure LMIC settings.
  - Support technical expert groups in developing guidance that addresses biases inherent in MI observational studies.
  - Evaluate field use situations for maternal RSV vaccine, such as year-round use in LMIC settings where RSV transmission is sustained.
- Evaluate the effect of RSV MI on anti-RSV antibodies in breastmilk.

2. Provide technical assistance to decision-makers and implementers in LMICs to inform introduction decisions and needs

OBJECTIVES: 1 B, 2 A, 2 B, 2 C, 3 B

- Provide technical assistance to LMICs on considering maternal RSV vaccine and feasible timing of introduction by adapting decision-making framework to relevant contexts (see near-term activity 10).
- Provide technical assistance to LMICs on maternal RSV vaccine procurement and supply requirements, and budget/financing/operations needs and timeframes.
- Provide technical assistance to LMICs in estimating cold chain and vaccine logistics requirements for maternal RSV vaccine.

3. Develop a global financing strategy to achieve optimal RSV MI delivery in LMICs

OBJECTIVES: 2 A, 2 C, 3 A

- Collate and disseminate data for donors on potential funding needs and RSV MI benefits, including delivery through an integrated platform.
- Support countries to identify funding mechanisms for integration support.

4. Conduct cost-of-illness (COI) studies in underrepresented geographies[i]

OBJECTIVES: 2 A, 2 C

- Compare RSV costs to potential proxies (e.g., pneumonia) to determine the need for additional studies.
- Collect data on how households finance RSV illness by wealth status as part of COI studies.

[i]Current work in progress includes two new RSV COI studies conducted by PATH and partners. Results from a PATH Malawi study are expected in 2018 or 2019. Site selection for additional studies is ongoing.

5. Evaluate RSV MI delivery costs and financing needs at the country level

OBJECTIVES: 2 A 2 C 3 A 3 B

- Conduct costing and budget impact analyses to determine country financing needs and inform vaccine introduction decision-making.
  - Assess financing needs in the context of immunization budgets, new vaccine introductions, and country transitions from Gavi.

PATH

SUMMARY AND RECOMMENDATIONS

Maternal RSV vaccines may be available in the next several years and have the potential to improve infant health and survival in LMICs. While much has already been achieved to support RSV MI decision-making and delivery, additional work remains. Due to the multi-faceted and complex nature of the work ahead, many activities outlined in this roadmap must begin now to ensure that maternal RSV vaccines meet global policy and financing requirements, countries can make informed decisions around introduction, and mechanisms are in place to optimize vaccine delivery and monitor safety. Wide-scale use of maternal RSV vaccines in LMICs will furthermore depend on many factors not yet guaranteed. Vaccines are still in development and compelling evidence will be needed for global and country decision-makers to prioritize maternal RSV vaccine amidst other public health priorities. Changes to health systems and services may also be needed to optimize vaccine delivery in LMICs.

The activities outlined in this roadmap require action to address essential and supportive needs identified in AMI's RSV MI gap analysis and prioritized by technical experts responding to an online survey. They build upon existing evidence, guidance, experience, and systems, and complement a number of current efforts in the field. Near-term activities address three overarching objectives:

- Ensuring the availability of safe, effective, and affordable maternal RSV vaccine.
- Enabling evidence-based global and country decision-making around maternal RSV vaccine.
- Enabling systems and services to routinely, efficiently, and equitably deliver maternal RSV vaccine.

Overall, the near-term activities outlined in this roadmap are urgently needed for RSV MI decision-making and LMIC delivery to move forward. They will generate disease burden, health economic, and vaccine impact data that inform global and country policy and financing decisions around RSV MI. They also support maternal RSV vaccine development, licensure, and monitoring to ensure that products meet safety, performance, and programmatic suitability requirements for LMICs and to achieve sufficient global vaccine supply. In addition, they support increased awareness of RSV and MI, which is important given observations of low RSV awareness and prioritization, particularly at the country level. Lastly, the activities are imperative to ensuring that countries optimize vaccine use once maternal RSV vaccines are available. The next step towards informed maternal RSV vaccine decision-making and rapid and efficient introduction and uptake in LMICs is to identify responsible parties for ensuring that specific pieces of this work are conducted in the timeframe needed, efforts are coordinated, and that results are shared with appropriate stakeholders.

Every family deserves to see their children survive and thrive no matter where they live. With maternal RSV vaccines on the horizon, the activities outlined in this roadmap are intended to help mothers and infants everywhere have every chance to benefit without delay when vaccines become available. AMI will update this roadmap annually as work progresses, additional evidence becomes available, gaps are filled, and new gaps are identified. We welcome input, which can be sent to **AMISecretariat@path.org**.

REFERENCES

1. PATH. *Advancing RSV Maternal Immunization: a Gap Analysis Report.* Seattle: PATH; 2018.Available at https://path.azureedge.net/media/documents/Advancing_RSV_Maternal_Immunization__A_Gap_Analysis_Report.pdf.
2. Hall CB, Weinberg GA, Iwane MK, et al. The Burden of Respiratory Syncytial Virus Infection in Young Children. *The New England Journal of Medicine.* 2016;360(6):588-598. doi:10.1056/NEJMoa0804877.
3. Hall CB, Geoffrey A. Respiratory Syncytial Virus – Associated Hospitalizations Among Children Less Than 24 Months of Age. *Pediatrics.* 2013;132(2):e341-8. doi:10.1542/peds.2013-0303.
4. Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower-respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *The Lancet*. 2017;390(10098):946-958. doi:10.1016/S0140-6736(17)30938-8.
5. World Health Organization. *RSV vaccine research and development technology roadmap: priority activities for development, testing, licensure and global use of RSV vaccines, with a specific focus on the medical need for young children in low- and middle-income countries.* Geneva: WHO; 2017. Available at: http://www.who.int/iris/handle/10665/258706. License: CC BY-NC-SA 3.0 IGO.
6. Global Alliance to Prevent Prematurity and Stillbirth (GAPPS). *Maternal Immunization Safety Monitoring in Low-and Middle-Income Countries: A Roadmap for Program Development.* Geneva: GAPPS; 2017.Available at: http://apps.who.int/medicinedocs/documents/s23275en/s23275en.pdf.
7. Modjarrad K, Giersing B, Kaslow DC, et al. WHO RSV Vaccine Consultation Expert Group. WHO consultation on Respiratory Syncytial Virus Vaccine Development Report from a World Health Organization Meeting held on 23-24 March 2015. *Vaccine.* 2016;34:190-7. Available at http://dx.doi.org/10.1016/j.vaccine.2015.05.093.
8. Caballero MT, Bianchi AM, Nuño A, Ferretti AJP, Polack LM, Remondino I, Rodriguez MG, Orizzonte L, Vallone F, Bergel E, Polack FP. Mortality in children in the community associated with acute respiratory infections. *The Journal of Infectious Diseases.* 2018; PMID:30165655 doi: 10.1093/infdis/jiy517. [Epub ahead of print].
9. VIEW-hub webpage. International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health website. Available at www.view-hub.org. Accessed September 26, 2018.
10. World Health Organization. *WHO Expert Committee on Biological Standardization: Guidelines on clinical evaluation of vaccines: regulatory expectations sixty-seventh report*. Annex 9 (WHO Technical Report Series, No. 1004;) Geneva: WHO; 2017 Available at http://www.who.int/entity/biologicals/expert_committee/WHO_TRS_1004_web_Annex_9.pdf?ua=.
11. Jones CE, Munoz FM, Spiegel HM, Heininger U, et al. Guideline for collection, analysis and presentation of safety data in clinical trials of vaccines in pregnant women. *Vaccine.* Available at https://www.ncbi.nlm.nih.gov/pubmed/27481360.
12. Moran AC, Moller AB, Chou D, et al. "What gets measured gets managed:"revisiting the indicators for maternal and newborn health programmes. *Reproductive Health.* 2018:18-19. doi:10.1186/s12978-018-0465-z.
13. Maternal Death Surveillance and Response (MDSR) webpage. World Health Organization website. Available at http://www.who.int/maternal_child_adolescent/epidemiology/maternal-death-surveillance/en/. Accessed on September 28, 2018.
14. INDEPTH Network website. Available at http://www.indepth-network.org/. Accessed September 28, 2018.
15. IMPRINT website. Available at http://www.imprint-network.co.uk/projects.html. Accessed September 28, 2018.
16. European Surveillance of Congenital Anomalies (Eurocat) website. Available at http://www.eurocat-network.eu/. Accessed January 4, 2018.
17. Latin American Colaborative Study of Congenital Malformations (ECLAMC) website. Avaiilable at http://www.eclamc.org/eng/index.php. Accessed January 4, 2018.

18. Vaccines and Medications in Pregnancy Surveillance System (VAMPS) webpage. American Academy of Allergy Asthma & Immunology website. Available at https://www.aaaai.org/about-aaaai/strategic-relationships/vampss Accessed September 28, 2018.

19. Folic Acid: Birth Defects (COUNT) webpage. Centers for Disease Control and Prevention website. Available at https://www.cdc.gov/ncbddd/birthdefectscount/basics.html Accessed January 4, 2018.

20. Child and adolescent health and development: New-born and Birth Defects (NBBD) Surveillance Initiative webpage. World Health Organization website. Available at http://www.searo.who.int/entity/child_adolescent/nbbd/web/en/ Accessed January 5, 2018.

21. Market shaping webpage. Gavi the Vaccine Alliance website. Available at https://www.gavi.org/about/market-shaping/. Accessed September 28, 2018.

22. Maternal, newborn, child and adolescent health webpage. World Health Organization website. Available at http://www.who.int/maternal_child_adolescent/topics/quality-of-care/network/en/. Accessed September 28, 2018.

23. Fleming JA, Baltrons R, Rowley E, Quintanilla I, et al. *I*mplementation of maternal influenza immunization in El Salvador: experiences and lessons learned from a mixed-methods study. *Vaccine.* 2018;36(28):4054-4061.

24. PATH. *Maternal Influenza Immunization: Lessons from vaccine introduction and use in El Salvador.* Seattle: PATH; 2016.

25. PATH. *Maternal Influenza Immunization: Perceptions of decision-makers, health care providers, and the community in Malawi.* Seattle: PATH; 2016.

APPENDICES

APPENDIX 1: GAP SUMMARY TABLE

Listed below are the gaps that the activities outlined in this RSV MI roadmap aim to fill and that were prioritized in a survey of more than 70 AMI and non-AMI experts. They include those identified in AMI's RSV MI gap analysis as 'essential and specific to MI' and 'essential across immunizations,' which must be filled for maternal RSV decision-making and/or introduction to move forward. They also include gaps categorized as 'non-essential but supportive,' which, if addressed, could strengthen advancement, but are not required. Not included are gaps categorized as 'non-essential and peripheral,' which may be of interest, but do not need to be addressed to move forward. Note that within categories, the gaps are not in order of individual priority.

#	Gap Description
Essential and specific to MI	
1	RSV burden of disease data stratified by narrow age bands for infants and collected in hospital and non-urban settings without access to hospitals in low- and middle- income countries (LMICs). Limited data currently available in publication and in gray literature should be consolidated and disseminated.
2	Evidence of maternal vaccine effect against severe RSV disease in infants to support licensure/marketing approval and inform cost-effectiveness analyses. Data should include immunogenicity, safety, efficacy, and duration of infant protection.
3	Additional data on the effect of maternal co-morbidities and preterm birth, RSV vaccine immunogenicity, maternal antibody transfer, and vaccine effectiveness.
4	Additional vaccine effectiveness, immune, and safety data to inform the potential for broadening the RSV vaccination window beyond that used in Phase 3 trials, particularly for regions where assessing gestational age is challenging and where ANC coverage during the second and third trimesters of pregnancy is low.
5	Data on the immune effect of maternal RSV vaccine co-administration with other maternal vaccines used in LMICs and effect of repeat vaccination across multiple pregnancies.
6	The costs associated with providing maternal immunization (MI) through antenatal care (ANC), including for vaccination strategies such as campaigns or outreach and those associated with strengthening the ANC infrastructure.
7	Identifying funding mechanisms for supporting RSV MI integration between Expanded Programme on Immunization (EPI) and ANC to enable development of plans and timing for vaccine introduction.
8	Information and data across settings on current mechanisms and modalities for ANC delivery and their capacity to routinely deliver vaccines.
9	Information on appropriate management models and effective coordination mechanisms between EPI and maternal, newborn, and child health (MNCH) programs to drive decision-making, strategy development, and effective implementation of RSV MI.
10	Defining cold chain, logistical, and vaccine management requirements and processes for maternal RSV vaccines.
11	Data on the impact of integrating RSV MI with existing ANC services on ANC quality and coverage.
12	Understanding the drivers and barriers for RSV MI acceptance and uptake in LMIC contexts.
13	Evidence-based advocacy and communications strategies tailored to global, regional, national, and sub-national stakeholder interests, knowledge, perspectives, and concerns to support RSV MI policymaking, information-sharing, and demand generation.
14	Information on RSV disease and MI to support stakeholder awareness, engagement, and advocacy at regional and country levels.
15	Post-marketing studies and routine surveillance to further evaluate RSV vaccine safety and document adverse events following immunization (AEFIs) in pregnant women and their infants in LMICs, including those with co-morbidities.

#	Gap Description
16	Strengthened immunization monitoring and surveillance systems in LMICs to reliably track and report pregnancy and birth outcomes, vaccine coverage, and AEFIs.
17	Background rates on pregnancy outcomes in LMICs to facilitate maternal RSV vaccine safety data interpretation.
Essential across immunizations	
18	Collection of standardized data, including continuous variables, to allow comparison across studies regardless of case definition.
19	Improved capability for detecting RSV in LMICs in both hospital and non-urban settings without hospital access, to inform country demand and introduction decisions based on disease burden and for monitoring vaccine effect after introduction.
20	Funding support for RSV vaccine identified for Gavi-eligible and non-eligible LMICs.
21	Engagement and support of international partners for demand forecasting and evaluating and working with manufacturers to ensure sufficient, timely, sustainable, and affordable vaccine supply in LMICs.
22	Additional information on the cost of RSV illness in infants, children, and other risk groups or evidence of whether or not different respiratory illnesses might serve as a proxy. Specific needs include direct medical, direct non-medical, and indirect costs for inpatient, outpatient, and non-medically attended illness from both household and provider perspectives. This information should be representative of different geographies and is especially important for middle-income countries.
23	Additional information on vaccine cost, cost of delivery, and budget impact of RSV MI. Information is needed to link costing studies to budget impact and sustainability analyses. Whether the cost of delivery for other interventions is an appropriate proxy for RSV MI is unknown, which may vary by delivery platform/strategy.
24	Country- and/or RSV-specific cost-of-illness and cost-of-delivery data to inform country and/or regionally relevant cost-effectiveness studies. This will be important for country decision-making, including in non-Gavi eligible countries.
25	Clarity around Gavi-eligible and non-Gavi eligible countries' ability to afford the vaccines in their current portfolio.
Non-essential but supportive	
26	Data on the seasonal distribution of RSV in LMICs to inform optimal vaccine delivery strategies.
27	Additional evidence from LMICs on RSV seasonal variation, annual variation in disease incidence, transmission dynamics, RSV serogroup prevalence, and clinical treatment management standards.
28	Data on RSV disease burden in specific sub-populations to inform appropriate vaccination strategies for high-risk populations.
29	Assessment of vaccine impact on recurrent wheeze (up to five years of age) and asthma (greater than five years of age) in children of vaccinated mothers, including risk factors that interact with RSV disease or predispose to wheezing disorders.
30	Evidence of RSV vaccine effect on all-cause lower respiratory tract infection, co-infections with other pathogens requiring medical attention, and lobar (presumed bacterial) pneumonia from post-marketing studies.
31	Evidence on how households finance the costs of RSV illnesses, what fraction of cases lead to catastrophic health expenditures, and whether RSV illness costs vary by wealth status or other criteria.
32	Evidence on effective strategies to enhance impact and cost-effectiveness of RSV interventions in LMICs.
33	Current data from LMICs on the number and timing of ANC visits identifying visit timing after the first visit and visit frequency beyond the fourth visit.
34	Information on effective mechanisms for following up with women that miss visits or do not seek ANC in LMICs.
35	Strategies to improve vaccination coverage in women who do and do not receive ANC via the formal healthcare system, including missed vaccination opportunities.
36	Information on how the new WHO ANC guidelines are implemented and monitored in LMICs, with a focus on lessons relevant for the introduction of maternal RSV vaccines.
37	Additional evidence on appropriate framing and messaging of RSV MI for different stakeholder groups.

APPENDIX 2: AMI MEMBERS

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