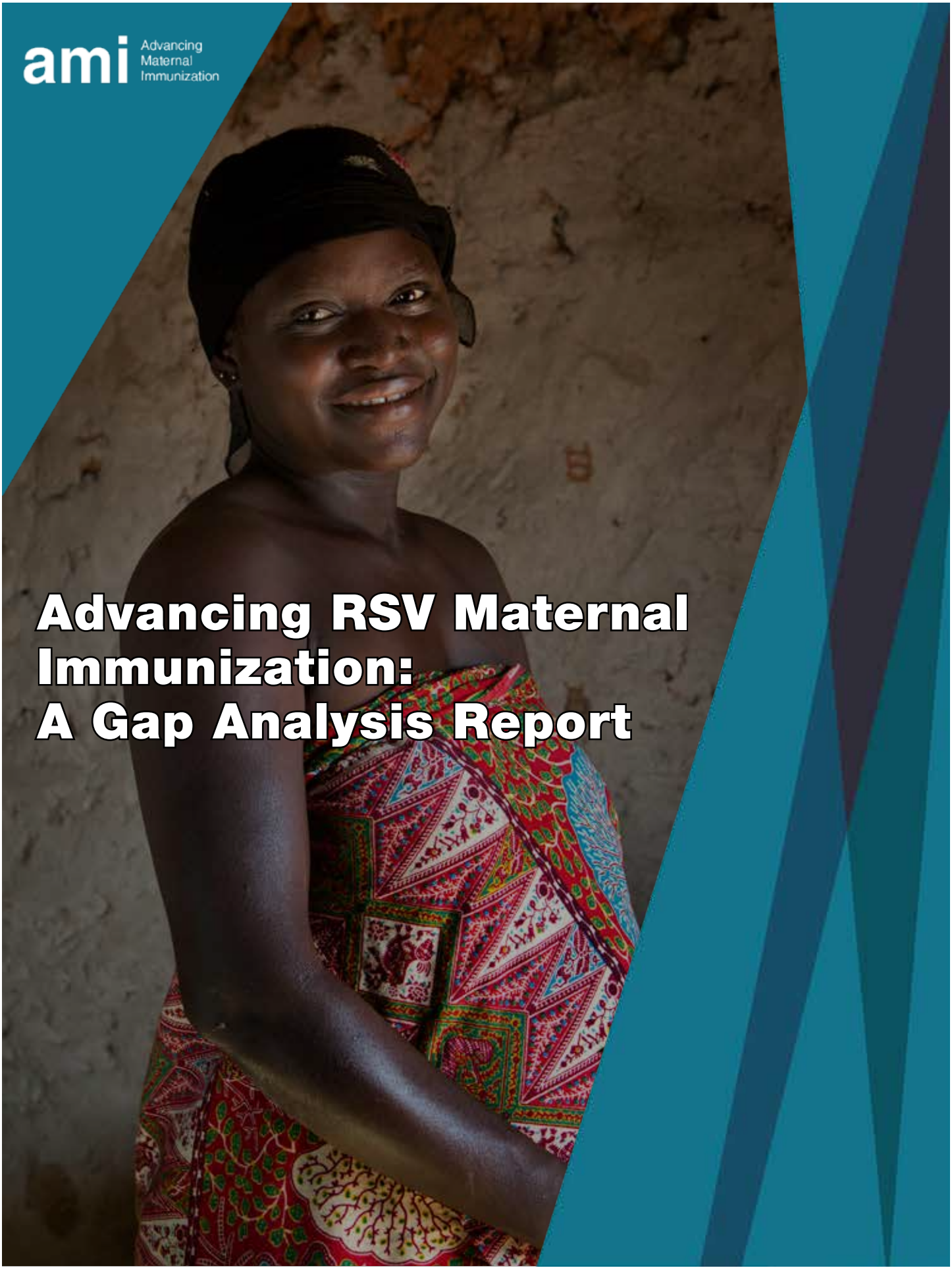
ami Advancing Maternal Immunization



Advancing RSV Maternal Immunization: A Gap Analysis Report

ACKNOWLEDGEMENTS

This work was built on critical 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 report. We also thank the individuals that 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 decision-makers, implementers, researchers, 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 RSV maternal vaccines, and to identify a strategy for meeting introduction and uptake requirements in LMICs.

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EXECUTIVE SUMMARY

Despite significant advances in child survival, deaths in the earliest months of life remain unacceptably high, particularly in low- and middle-income countries (LMICs). Neonatal mortality accounts for nearly half of all child mortality under five years of age and is declining at a slower rate than for children one through 59 months old.[1] Certain infections that threaten neonates and infants in the earliest months of life can be prevented by vaccinating pregnant women to provide immunity for themselves and their infants. This practice, maternal immunization (MI), gives a mother the opportunity to protect her child *in utero* and during the first vulnerable months following birth during which the child cannot receive most routine vaccinations. Multiple vaccines for MI are in development.[2] A maternal vaccine against respiratory syncytial virus (RSV)—an important cause of childhood acute lower-respiratory illness (ALRI)—is furthest along. This vaccine could be the first licensed RSV vaccine, the first vaccine specifically developed for administration to women during pregnancy with the purpose of protecting her infant, and one of the first vaccines targeted for near simultaneous introduction in high-, middle-, and low-income settings. Much needs to happen, however, for this intervention to reach its lifesaving potential.

MI has a safe and effective track record against pathogens such as tetanus, pertussis, and influenza.[3] It is an important component of a life course vaccination strategy; yet, it is not widely used beyond maternal and neonatal tetanus (MNT) prevention, particularly in LMICs. The MNT Elimination (MNTE) initiative, however, is not the ideal model for delivering maternal RSV vaccines, since it often augments routine vaccine delivery with costly and time-intensive supplementary immunization activities and has less stringent target population and administration requirements.

In light of possible RSV interventions on the horizon, this report describes the evidence, information, and policy needs of global and country decision-makers, public health program planners, and implementers who might be involved in decision-making or introducing maternal RSV vaccines. The report focuses specifically on the context of potential introduction in LMICs. Developed by the Advancing Maternal Immunization (AMI) collaboration, it focuses on maternal RSV vaccines and summarizes relevant evidence across the following broad topic areas: 1) disease, 2) product, 3) health economics and financing, and 4) vaccine service delivery. The report highlights critical gaps in evidence that, if left unfilled, could delay or preclude vaccine introduction in LMICs.

Coordinated by PATH and the World Health Organization (WHO), AMI is a collaboration among 62 diverse experts from around the world and across immunization and maternal, newborn, and child health (MNCH) fields. As a follow-on to the gap analysis and this report, AMI will develop a consensus-driven RSV MI roadmap to help funders, implementers, and countries understand the next steps and timing around maternal RSV vaccine introduction in LMICs.

Gap analysis findings

RSV disease

Researchers have studied RSV for decades, providing data on disease symptoms, treatment, and acute sequelae. Most of this data, however, is from high-income countries (HICs).[4] This evidence stands in contrast to the RSV burden distribution. A recent global disease burden study modelled data from 329 studies of laboratory-diagnosed RSV-ALRI and estimated 33.1 million (uncertainty range 21.6-50.3) annual episodes of RSV-ALRI globally in children aged less than five years.[5] Of these, an estimated 30.5 million (uncertainty range 19.5-47.9) episodes occurred in LMICs, marking a disproportionate burden relative to the geographic distribution of the under-five population.

Collection of and access to RSV disease data from LMICs is improving, but additional data and granularity are needed, particularly on disease in the first six months of life.[6] Improved RSV surveillance in LMICs would strengthen understanding of the need for RSV interventions. To accomplish this, many countries, particularly low-income countries (LICs), need improved diagnostic capacity to gather age-stratified disease data to better characterize RSV disease among pregnant women and infants and provide additional information on RSV transmission, sequelae, and the impact of co-morbidities on disease. An ongoing Novavax phase 3 (Ph3) trial of the leading maternal RSV vaccine candidate will provide data on disease in both pregnant women and their infants' first year of life. Additional studies, however, will be needed to determine the effectiveness of RSV MI in LMICs.

Product

While much is known about managing RSV disease in neonates and infants, options for RSV prevention are limited. Passive prophylaxis can protect infants at risk for severe RSV disease.[7–9] The only licensed RSV prophylactic is palivizumab (Synagis®), a monoclonal antibody (mAb). A 2013 meta-analysis calculated a 51% (36-63%) reduction in the risk of RSV hospitalization in preterm and medically high-risk infants receiving palivizumab compared to placebo.[10] While effective, monthly injections throughout RSV season and the high cost of palivizumab limit its use in LMICs, necessitating additional options for RSV disease prevention. Nonetheless, the effectiveness of the mAb and evidence that maternal RSV antibody provides similar protection to the infant support the rationale for vaccination in pregnancy.[10–13]

Forty vaccines and four mAbs are currently in development, with 18 in clinical trials.[2,14] The most advanced is the Novavax RSV Fusion-protein (RSV F) vaccine candidate, which is being evaluated for use in pregnant women and could reach licensure by late 2020 or early 2021.[15] Gavi, the Vaccine Alliance (Gavi) will consider investment in RSV vaccines for its 2018 Vaccine Investment Strategy.

Novavax will generate immunogenicity, safety, and efficacy data to support licensure and marketing approval for its maternal RSV vaccine. Additional studies will be needed to further evaluate vaccine effectiveness in LMICs, the effects of maternal co-morbidities and preterm delivery on RSV vaccine immunogenicity and maternal antibody transfer, and the effectiveness of repeat vaccination across multiple pregnancies. In addition, post-marketing studies and routine surveillance will be needed to further evaluate vaccine safety and document adverse events following immunization (AEFI).

WHO provides tools to guide development and RSV vaccine testing. The WHO Preferred Product Characteristics (PPC) for RSV vaccines provides specific guidance to vaccine manufacturers on developing a candidate that is suitable for use in LMICs and is an aid for WHO prequalification (PQ). The lead maternal RSV vaccine candidate aligns with many of these parameters. In addition, the Antiserum to Respiratory Syncytial Virus WHO 1st International Standard is now available for harmonization of RSV neutralization assay data, allowing comparison of antibody responses across studies and vaccine candidates.[16]

RSV MI economics, impact, and financing

Health economics and financing information are critical components of evidence needed for global and country decision-making and implementation planning for RSV MI. Gavi is a key stakeholder and currently the most likely source of external financing to support RSV vaccination in LMICs. Without Gavi support, LMICs are less likely to introduce any new vaccine. Health economics analyses can show which interventions are impactful, affordable, resource efficient, and financially sustainable. At this time, however, insufficient economic data are available regarding RSV in LMICs, such as cost of RSV illness, vaccine cost, cost of delivery, cost-effectiveness, budget impact, and affordability.

Several initiatives have and will contribute to the needed data. A recent RSV cost-of-illness study in Malawi and similar planned studies for under-represented regions will complement existing data. Cost-of-illness data for other diseases may also be able to serve as a proxy. Existing WHO economic guidance and tools to assess maternal influenza immunization contribute cost-of-delivery data and information relevant for RSV. Information from other antigens may also provide insight into delivery costs. Furthermore, in 2018, PATH completed a maternal RSV vaccine demand forecast and several organizations conducted RSV impact modelling in LMICs and provided health impact estimates to Gavi with cost-effectiveness estimates to follow.[17] Additional economic evidence is needed, but this work can proceed from a strong base.

Maternal RSV vaccine service delivery in LMICs

To ensure effective implementation of national RSV MI programs and maximize impact, it is imperative to develop acceptable, feasible, and sustainable introduction and use strategies. The MNTE experience in many LMICs suggests that immunization service delivery to pregnant women is often insufficient to achieve desired coverage levels and that sustainability and impact will require a comprehensive approach.[18,19] To achieve desired impact in a sustainable manner, delivery strategies, guidelines, tools, and recommendations will need to be designed with countries to account for health systems and local religious, cultural, political, and social factors.[20]

Effective delivery of RSV MI in LMICs will require antenatal care (ANC) and Expanded Programme on Immunization (EPI) program managers to expand or modify service delivery, logistics, and management plans. In LMICs, ANC is a natural entry point for delivering several essential interventions to pregnant women in a timely manner, including MI. Likewise, EPI platforms are well-established and functional in most LMICs, presenting opportunities for integration and cooperation between EPI and ANC, although difficulties are to be expected, particularly given challenges in current ANC coverage and continuity of care.[21]

In addition, stakeholder engagement using evidence- and value-based advocacy and communications (A&C) strategies will play a major role in awareness, perceptions, and acceptability around RSV and MI and generating vaccine demand.[22] This will entail comprehensive stakeholder mapping, localized A&C strategies, and an understanding of baseline knowledge, awareness, perceptions and acceptability. In addition to the MNTE and maternal influenza vaccination experiences, existing guidelines, recommendations, and best practices can help inform these strategies.

Finally, safety monitoring and ethical considerations are crucial in the MI context. In the case of maternal vaccines, the assessment of vaccine safety should include the collection of baseline data around adverse pregnancy events prior to vaccine introduction. A strong evidence base around safety would also pre-emptively address potential risk perception, management of risk communication, and vaccine hesitancy issues. From an ethics perspective, MI gives a mother an opportunity to protect her child—and in some cases, herself—a frame potentially important for advocacy and demand generation. However, there is a need to move from a risk-based approach to one where the interests of expectant mothers assume centrality. Lastly, RSV delivery provides a unique opportunity to educate mothers and reinforce vaccine messaging throughout the life course.

Overarching themes

In an increasingly crowded vaccine landscape, global, national, and local decision-makers will require the information called for in this report to make informed decisions about RSV MI. While some evidence is currently available or in the process of being generated, work remains to be done. The full collection of gaps described in this report represent the breadth of information required, but their essence falls into three overarching themes.

Awareness and perceptions

Awareness and perceptions of RSV and maternal vaccines will drive decision-making around vaccine introduction as well as acceptability and uptake of maternal RSV vaccines. While pervasive, RSV disease remains largely unrecognized, particularly at the country level. Decision-makers will require nuanced RSV disease burden data from LMICs to understand the potential impact of a maternal RSV vaccine when prioritizing interventions. A strong value proposition for maternal RSV vaccine will also be needed, and decision-makers will need to consider its cost-effectiveness, budget impact, and affordability.

Concerted effort will be required to improve knowledge and awareness of RSV disease and protection strategies, including MI, among healthcare workers, pregnant women, and their key influencers. Appropriate strategies for communicating information to generate demand will also require understanding community and provider perceptions to tailor information appropriately to local contexts.

Improved monitoring of pregnancy outcomes and safety surveillance

Strengthening or instituting systems *de novo* to monitor health outcomes in pregnant women and newborns before vaccine introduction is needed to provide critical baseline data for risk attribution and inform strategies around risk communication and vaccine hesitancy. Once the vaccine is introduced, robust pharmacovigilance and adverse events monitoring and reporting will be needed.

Localized delivery strategies

The global introduction of a novel maternal RSV vaccine will require countries to tailor strategies and mechanisms for vaccine delivery to their individual contexts. Given the target population, this will most likely require coordination between EPI and MNCH stakeholders and may necessitate modifications to current service delivery, logistics, and management systems. While there are lessons to be learned from other experiences, information will be required to identify optimal delivery models across contexts and inform harmonization across capacity building, management, and reporting structures. Identifying sustainable financing mechanisms will also be critical.

Keeping in mind the unique nature of maternal RSV vaccines, the critical evidence gaps in this report have been categorized as either "essential and specific to maternal immunization," which are unique to MI or "essential across immunizations", which are generally applicable across vaccines. In total, we identified 9 essential evidence gaps. While this is significant, numerous efforts are currently generating data that will fill or contribute data to many of these gaps by the time a maternal RSV vaccine receives WHO recommendation. Nonetheless, new efforts will be needed to address remaining gaps identified in this report. As the RSV landscape continues to evolve, the work already in progress and additional data called for here will support efforts to navigate the pathways and solutions for preventing RSV disease to help infants survive and thrive, no matter where they live.

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LIST OF ABBREVIATIONS

A&C	Advocacy and communications
AE	Adverse event
AEFI	Adverse events following immunization
ALRI	Acute lower-respiratory illness
AMI	Advancing Maternal Immunization collaboration
ANC	Antenatal care
BCC	Behavior change communication
CFR	Case fatality rates
CLD	Chronic lung disease
CHD	Congenital heart disease
CRVS	Civil Registration and Vital Systems
DALY	Disability-adjusted life year
ELISA	Enzyme-linked immunosorbent assay
EPI	Expanded Programme on Immunization
ERD	Enhanced respiratory disease
FDA	US Food and Drug Administration
FI-RSV	Formalin-inactivated RSV
GISRS	Global Influenza Surveillance and Response System
HDSS	Health and demographic surveillance systems
HIC	High-income country
hMPV	Human metapneumovirus
IgA	Immunoglobulin A
IgG	Immunoglobulin G
KOL	Key opinion leader
LIC	Low-income country
LMIC	Low- and middle-income countries
mAb	Monoclonal antibody
MNCH	Maternal, newborn, child health
MNCAH	Maternal Neonatal Child and Adolescent Health
MI	Maternal immunization
MIACSA	Maternal Immunization and Antenatal Care Situation Analysis
MNT	Maternal and neonatal tetanus
MNTE	Maternal Neonatal Tetanus Elimination
MPDSR	Maternal and perinatal death surveillance and response
NGO	Non-governmental organization
NITAG	National Immunization Technical Advisory Group
PCR	Polymerase chain reaction
Ph3	Phase 3 clinical trial
PPC	Preferred product characteristics
PQ	Prequalification
PV	Pharmacovigilance
RITAG	Regional Immunization Technical Advisory Groups
RSV	Respiratory syncytial virus
RSV MI	Respiratory syncytial virus maternal immunization
RSV-ALRI	Respiratory syncytial virus-attributed acute lower respiratory illness
SAE	Severe adverse event
SAGE	World Health Organization's Strategic Advisory Group of Experts
SL	Strategic Leadership
TAG	Technical Advisory Groups
TEP	Technical Expert Panel
TT	Tetanus toxoid
UN	United Nations
UNICEF	United Nations Children's Fund
VIS	Vaccine Investment Strategy
WHO	World Health Organization
WG	Working group

1 INTRODUCTION

Despite reductions in neonatal and infant mortality, deaths and illnesses in these young age groups remain unacceptably high worldwide.[23] Public health interventions, including immunization, can prevent many of these outcomes.[24] Vaccinating pregnant women to protect themselves and their infants, or maternal immunization (MI), has emerged as a promising intervention against some infections that pose particular risk to newborns, infants, and mothers. It is an opportunity for a mother to protect her child during the vulnerable time between birth and when the child can receive and develop immunity from most routine vaccinations. Respiratory syncytial virus (RSV) is a pathogen targeted by this approach.

PATH/Eric Becker

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RSV is a common cause of acute lower respiratory illness (ALRI) in children younger than five years of age. Infants with ALRI attributed to RSV (RSV-ALRI) in the first months of life are most severely affected.[5] RSV disease disproportionately affects children in low- and middle-income countries (LMICs), where roughly 92% of RSV-ALRI occurs. Nearly half of RSV-ALRI deaths happen in the first six months of life—almost all of which occur in LMICs.[5] A monoclonal antibody (mAb), palivizumab, prevents serious RSV-ALRI in high-risk children, but its high cost and monthly dosing are barriers to broader use, especially in LMICs. No RSV vaccines are yet approved for use, but numerous candidates are in development. Some of these vaccine candidates are intended for MI to passively protect infants from RSV during the first high-risk months of life.

MI has a safe and effective track record against certain pathogens such as tetanus, pertussis, and influenza. In addition to RSV, new maternal vaccines are in development against other pathogens, including Group B *Streptococcus*.[3] While MI has potential to improve infant health and survival in LMICs, it is not widely used beyond maternal and neonatal tetanus (MNT) prevention. The Maternal and Neonatal Tetanus Elimination (MNTE) initiative is not the ideal model for delivering maternal RSV vaccine, however, since it uses supplementary immunization activities such as vaccination campaigns in many settings to augment routine vaccine delivery. There are also differences in target populations, vaccine administration windows, and dosing schedules. A platform for routinely delivering vaccines to pregnant women in LMICs, including RSV vaccine, will be needed to sustainably and equitably reach this population. In such a strategy, MI supports global strategies and objectives related to health and equity, including the Sustainable Development Goals and Universal Health Coverage.[25,26]

A maternal RSV vaccine, if and when licensed, would be the first approved RSV vaccine, the first vaccine specifically developed for MI with a label 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. Given that pregnant women fall outside the population targeted by the Expanded Programme on Immunization (EPI) and experience gained from other new vaccine introductions may not directly apply to maternal RSV vaccines, specific evidence will be required for global and country decision-making around this vaccine, including data that aid global and country policy, financing, and budget planning. Furthermore, countries must see a comparative value

in this vaccine and support the development of delivery strategies to ensure its rapid launch and equitable uptake. This will be a challenge for RSV MI, where familiarity with the disease is very low in LMICs, resulting in almost no demand for the vaccine at the present time.

Furthermore, while progress over the past 10 to 15 years in LMIC vaccine introductions through Gavi has helped improve child health and survival, current vaccine portfolios are difficult for many of these countries to fully implement and sustain.[27] Even with relatively high demand for Gavi vaccines, adding new vaccines and achieving coverage goals are ongoing challenges in these settings where there are many competing priorities in health and beyond. Generating the demand for and capacity to implement RSV MI in this environment will need to be addressed, particularly given the relative lack of current familiarity with and prioritization of RSV disease in LMICs.

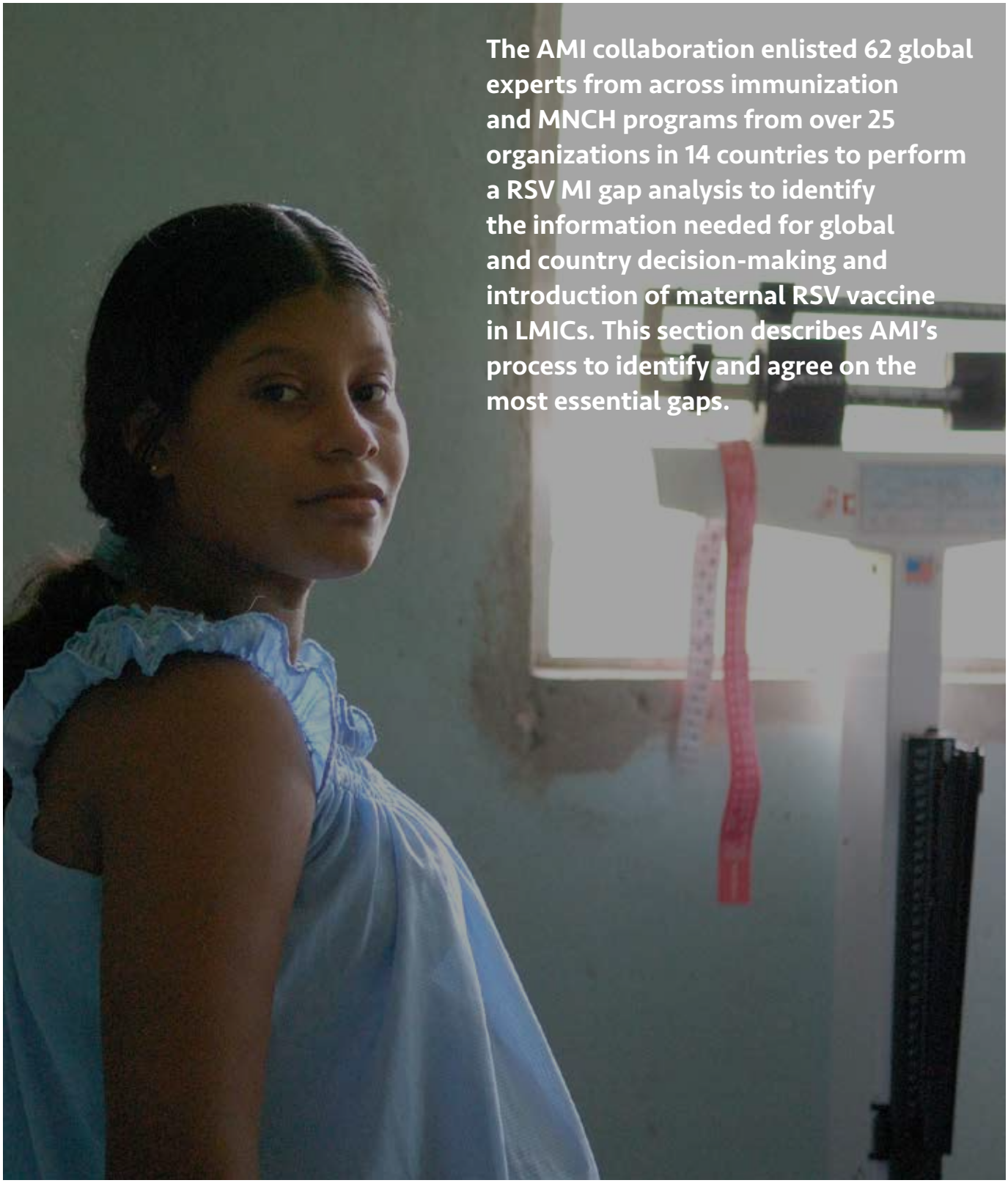
Launched in 2017 and coordinated by PATH and the World Health Organization (WHO), the Advancing Maternal Immunization (AMI) collaboration is a partnership of diverse experts from around the world and across immunization and maternal, newborn, and child health (MNCH) programs to identify viable pathways for informed RSV MI decision-making and introduction. In 2017/2018, AMI experts conducted a gap analysis to identify the information and conditions required for efficient maternal RSV vaccine decision-making and successful introduction in LMICs. This report outlines the findings of that gap analysis.

OBJECTIVES

The objectives of the gap analysis are to identify the information and conditions that will be needed to inform global and country decision-making and introduction of maternal RSV vaccines in LMICs. While this report focuses on maternal RSV vaccines, the analysis takes into consideration mAbs as an alternative prevention measure where applicable. The report briefly summarizes existing evidence and conditions across the following broad topic areas: 1) disease, 2) product, 3) health economics and financing, and 4) vaccine delivery. Finally, it highlights critical gaps in evidence that, if left unfilled, could delay or preclude vaccine introduction in LMICs. Gaps included are constrained to those deemed either essential or supportive to strengthening or accelerating global and country RSV MI decision-making and/or introduction. The primary audiences of this work are funders of global public health, policy decision-makers, researchers, vaccine developers, and country public health program implementers.

This report is the first piece of a two-part product. Key findings of this gap analysis will guide the development of a RSV MI roadmap, which will describe the activities and efforts needed to generate and assemble the evidence essential to optimize RSV MI. The roadmap will also propose a timeline for implementing those activities. The roadmap will be a resource to help funders, implementers, and countries understand the groundwork needed for maternal RSV vaccine decision-making and introduction.

2 METHODS



The AMI collaboration enlisted 62 global experts from across immunization and MNCH programs from over 25 organizations in 14 countries to perform a RSV MI gap analysis to identify the information needed for global and country decision-making and introduction of maternal RSV vaccine in LMICs. This section describes AMI's process to identify and agree on the most essential gaps.

PATH/Mike Wang

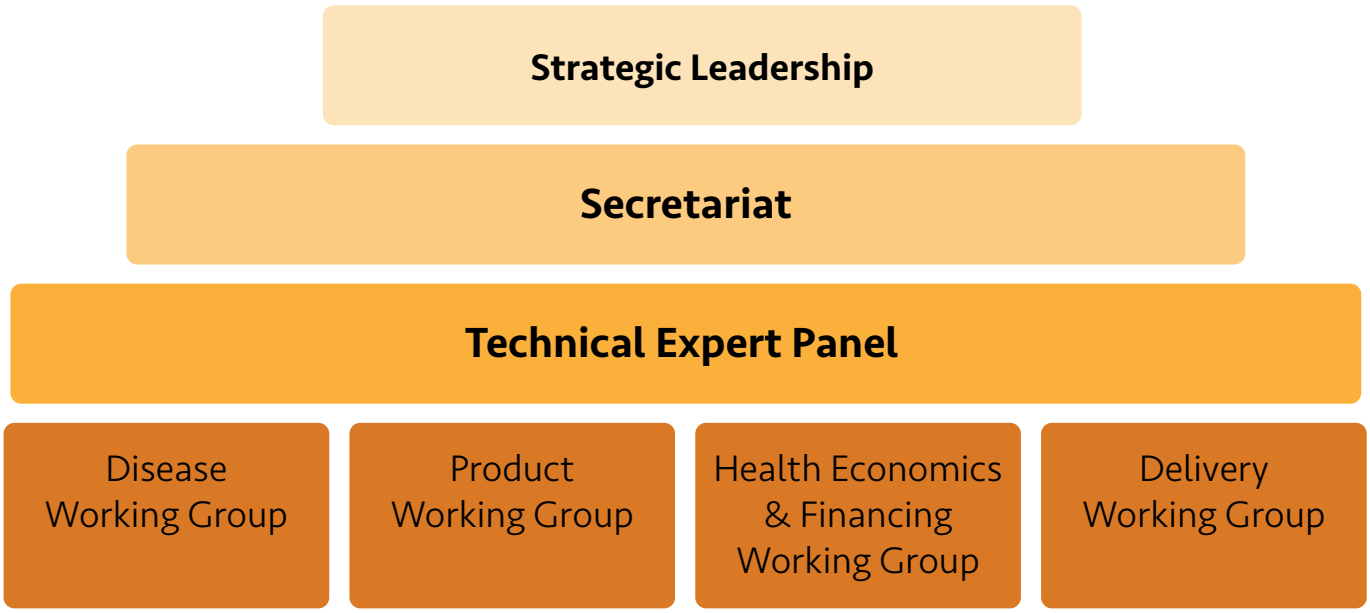
STAGE 1: BUILDING THE AMI STRUCTURE

AMI is comprised of four distinct groups with unique roles (see Figure 1)—Strategic Leadership (SL), Secretariat, Technical Expert Panel (TEP), and Working Groups (WGs). The SL, composed of five leaders from WHO and PATH with expertise in vaccine development, vaccine delivery, and MNCH, provides strategic direction for AMI. The Secretariat, housed at PATH, provides day-to-day support to AMI through technical and administrative oversight, coordinating member inputs, and finalizing products. For this gap analysis, the TEP defined the information required for vaccine decision-making and introduction, provided expert opinion on gap priorities, and reviewed documents produced by AMI. TEP expertise included vaccine licensure and WHO prequalification (PQ), subject matter expertise (including MI and RSV), MNCH, global vaccine policy and financing, LMIC public health decision-making, and program implementation. Finally, WGs included technical experts (from academia and research organizations), country decision-makers, and practitioners from across MNCH, immunization, and other relevant sectors. WG members conducted background research on specific topics, summarized existing evidence, and identified gaps in the evidence and conditions relative to RSV MI decision-making and introduction. (For a full list of AMI members, see Appendix 1.)

The Secretariat identified and recruited AMI members through a rigorous vetting process and invited candidates to participate according to their primary expertise, relevant experience, and training. The Secretariat took care to ensure diversity in terms of gender, global and LMIC perspectives, and technical skills. The Secretariat recruited members for the following working groups:

- **Disease WG (nine members)**—focused on RSV burden of disease in infancy and pregnancy and factors pertinent to informing the potential use and utility of a maternal RSV vaccine in LMICs.
- **Product WG (eight members)**—focused on key maternal RSV vaccines and immune parameters that inform decision-making around use in immunization programs and clinical evaluations; safety and pharmacovigilance (PV); RSV long-term sequelae; and meeting LMIC vaccine supply needs.
- **Health economics and financing WG (eight members)**—focused on RSV cost of illness; costs of intervention delivery; demand, impact, and cost-effectiveness; and financing and budget impacts of the vaccine in LMIC contexts.
- **Delivery WG (15 members)**—focused on health systems and patient, provider, and community factors relevant to maternal RSV vaccine introduction and uptake in LMICs, including policy considerations; key stakeholder awareness, perceptions, and acceptability;

FIGURE 1. **Advancing Maternal Immunization (AMI) structure**



vaccine logistics and supply chain; care-seeking and care-provision in pregnancy; health systems; and ethical, cultural, and gender issues relevant to vaccine uptake.

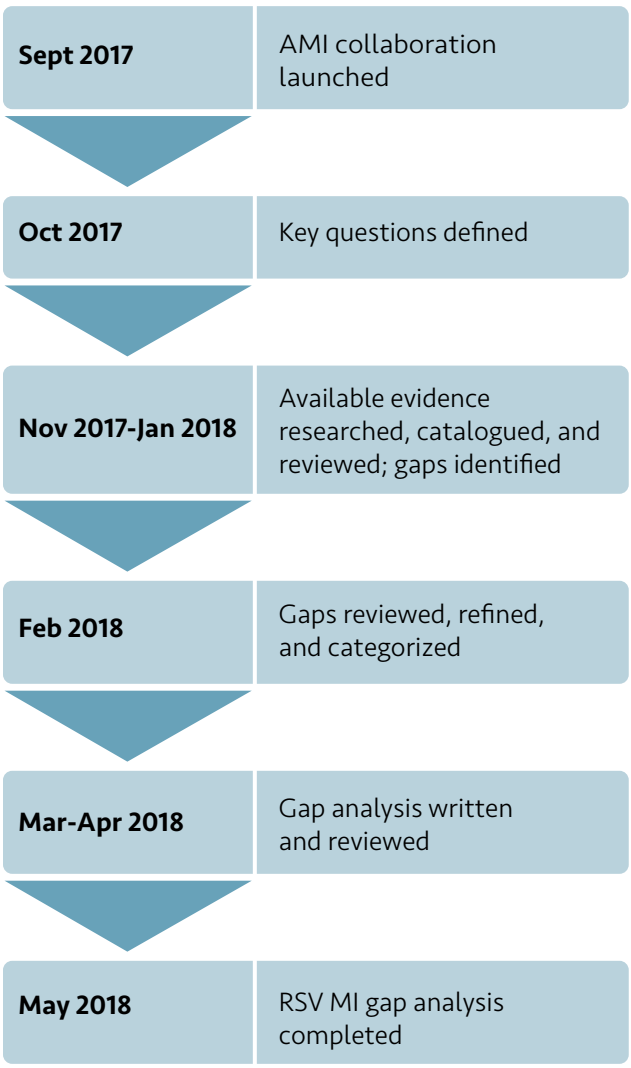
PATH officially launched the AMI collaboration in September 2017. Given the number of members and their geographic locations around the world, the Secretariat created a web-based platform called the RSV MI Knowledge Center to share information among AMI members, enhance member coordination, and promote transparency around processes and decision-making. The platform increased the visibility of the work and facilitated real-time sharing and discussion within and across working groups. The Knowledge Center also allowed members to cross check completeness and accuracy of compiled evidence and gaps.

STAGE 2: IDENTIFYING AND REFINING KEY QUESTIONS

The Secretariat used the 2015 WHO Strategic Advisory Group of Experts (SAGE) "Guidance document for the development of evidence-based vaccination-related recommendations" to develop an initial list of key questions and information needs anticipated to drive RSV MI decision-making at global and country levels.[28] The Secretariat compiled a final list of 99 questions after multiple rounds of review by the SL, TEP, and WG members. The Secretariat strove to limit the questions to those required for RSV MI decision-making and introduction in LMICs and then assigned key questions to relevant WGs. Within those WGs, individual AMI members known as 'question leads' further refined their assigned specific question(s) for clarity and to avoid duplication. Additional AMI members with relevant expertise and interest served as first-line reviewers for each question. (See Appendix 2 for a list of final key questions.)

STAGE 3: DOCUMENTING CURRENT EVIDENCE

Question leads managed the compilation and synthesis of existing evidence, information, or relevant conditions for their specific question(s). They gathered information using a combination of literature reviews (including peer-reviewed literature, gray literature, published and unpublished reports, and publicly available guidelines); key informant interviews; and expert opinion. Question leads collated findings into a template called a gap analysis framework. (See Appendix 3 for gap analysis framework templates.) Completed frameworks with full reference lists are available upon request.



Question leads evaluated the degree to which the available evidence for each question was sufficient to inform decision-making and introduction of RSV MI in a LMIC context. They evaluated the evidence by subject, generalizability, context and location, consistency, overall quality, and relevant limitations or biases. If the evidence for the question was considered *sufficient*, no gaps were identified. If the evidence was considered *insufficient*, question leads articulated specific gaps in the evidence that were essential for decision-making and/or introduction. (See Appendix 4 for a full list of identified gaps.) Question leads also identified relevant ongoing work that could provide evidence to fill the gaps. First-line reviewers reviewed and provided feedback on the gap analysis frameworks and specific gaps. As necessary, question leads sought additional ad hoc input from

PATH/Georgina Goodwin

external parties. This approach, facilitated through the Knowledge Center, garnered a collaborative and iterative review of the work across disciplines.

The topics that the AMI collaboration reviewed are expansive. While effort was made to limit duplication, WGs examined aspects of the same topic using different perspectives in some cases. For example, vaccine supply and demand issues, safety and surveillance, and disease burden were all considered by more than one WG. As the different lenses used for a topic may have resulted in different emphasis and/or perspectives for a common gap, each relevant issue is included in its respective WG section under the Results section. This overlap highlights the crosscutting and interconnected nature of some issues as they relate to global and country decision-making and introduction.

STAGE 4: ASSESSING GAPS

AMI characterized seven of the 99 questions as having sufficient information. For the remaining 92 questions, AMI identified unmet needs essential for decision-making and introduction, termed "gaps," across the four WGs. With input from WG members, The Secretariat removed duplicates, consolidated gaps by topic, and categorized them according to their criticality to RSV MI decision-making, RSV introduction in LMICs, and uniqueness to the MI space (see Table 1).

The SL and TEP reviewed the categorized gaps and provided additional context and suggestions to improve clarity and refine scope. The final list totaled 57 gaps across all categories, including 17 gaps essential and specific to MI; 12 gaps essential across immunizations; 21 non-essential but supportive gaps; and 7 non-essential and peripheral. In some cases, similar gaps were identified across WGs. These overlapping gaps were maintained to preserve the unique perspectives of each group and to highlight their crosscutting nature. Gaps are discussed in detail in the Results section of this report. The non-essential and peripheral gaps are listed in Appendix 4 and not described further in this document. Overall, we used a collaborative and iterative process to identify and describe the gaps; however, this methodology has some limitations, which are explored further in the Conclusion section of this report.

TABLE 1: **Gap categories and their definitions**

Gap category	Definition
Essential and specific to MI	A gap in information or conditions that is unique to MI and that must be addressed for MI decision-making and/or introduction to move forward.
Essential across immunizations	A gap in information or conditions that is generally applicable across vaccines (maternal and infant) and that must be addressed for MI decision-making and/or introduction to move forward.
Non-essential but supportive	A gap in information or conditions that, if addressed, could strengthen or accelerate MI decision-making and/or introduction, but is not required to move forward.
Non-essential and peripheral	A gap in information or conditions that may be of interest, but does not need to be addressed to advance, strengthen, or accelerate MI decision-making and/or introduction.

3 RESULTS

This section describes AMI's RSV MI gap analysis findings. These results summarize current evidence or conditions in the following broad topic areas: 1) disease, 2) product, 3) health economics and financing, and 4) vaccine delivery. Specific gaps identified as essential and specific to MI, essential across immunizations, and non-essential but supportive are listed at the end of each section. Some gaps are relevant to multiple topic areas and may appear more than once.

Paul Joseph Brown/GAPPS

9.1 DISEASE

This section summarizes what is known and unknown about RSV disease and its epidemiology, primarily pertaining to MI. It includes clinical manifestations, disease management, RSV-ALRI epidemiology, and risk factors for morbidity and mortality. Although this analysis focuses on infants, it also includes information relevant to older children and pregnant women. While RSV disease has been researched for more than five decades, most evidence is from high-income countries (HIC), although more recently, information has become available on disease patterns in a number of LMICs. However, for LIC contexts, the numbers of individual studies are not adequate for statistically interpreting risk factors, including co-morbidities and age strata.

RSV is a pneumovirus in the family *Paramyxoviridae*. It has a single-stranded, negative-sense genome of about 15 kilobases with 10 gene start sites that encode 11 proteins. Three of those proteins are displayed on the viral envelope. The small hydrophobic protein is a pentameric ion channel; the putative attachment protein (G) is a heavily O-glycosylated mucin-like glycoprotein; and the fusion glycoprotein (F) is responsible for mediating viral entry through pH-independent membrane fusion from without. The two major virus subtypes are A and B, which are largely defined by genetic variation in the G glycoprotein. Compared to other RNA viruses, RSV exhibits relatively little antigenic variation.[29]

RSV is a RNA virus with a pathogenic predilection for the human respiratory tract.[30] The only known animal reservoir for human RSV is the chimpanzee, and RSV infection is only semi-permissive in all reported animal models (African green monkey, baboon, bovine, murine, cotton rat, guinea pig), requiring a large virus inoculum to establish infection.[31] While RSV can cause upper respiratory infection alone, it commonly causes ALRI, albeit often mild. RSV-ALRI can lead to bronchiolitis and pneumonia, which are significant sources of morbidity and mortality among young children, especially infants up to one year of age.[4,32]

RSV infection is prevalent worldwide and has been shown to circulate continuously in tropical and subtropical countries such as Colombia, Malaysia, Qatar, Jordan, Yemen, and Taiwan, but with a seasonal pattern lasting five to nine months in most years.[33] The temperate zone pattern is more restricted to seasonal occurrence with typical seasons of three to five months. The concept of RSV outbreaks or epidemics is therefore predominately related to seasonal variation in temperate zones (and to a lesser extent, in the tropics) rather than the occurrence of unpredicted events. A single infection is not protective against subsequent infection, leaving individuals with the potential for multiple infections over time. Evidence does exist to indicate, however, that multiple infections may provide partial immunity and lead to less severe disease over the life time as airways grow and are less likely to be blocked by inflammatory debris.[34]

Clinical characteristics

RSV is the most common cause of serious ALRI in infants and young children and a significant cause of disease in the elderly and immunocompromised. Summarized here, however, are the clinical manifestations, disease management, and diagnostic features of RSV disease primarily pertaining to infants and the major manifestation of bronchiolitis. The discussion then focuses in on the possible relevance of these factors to RSV MI.

KEY HIGHLIGHTS: RSV CLINICAL CHARACTERISTICS, TRANSMISSION, TREATMENT, AND SEVERITY

Progress

- RSV disease symptoms, supportive care, and currently available treatment options are well understood.

Work remaining

- Additional options for RSV prevention are needed.
- Evidence is needed from studies designed and powered to evaluate the effect of RSV prevention in early infancy on subsequent wheezing illness.

Existing and missing evidence or conditions on the ground

While available clinical data come disproportionately from HICs, limited data from LMICs suggest that the RSV manifestations, diagnosis, and treatments are similar to those in HICs. As discussed below, additional studies are needed on RSV transmission, disease sequelae, and severity in LMICs (and LICs in particular).

Symptoms and diagnoses

RSV symptoms begin four to six days after infection, often with nasal congestion, rhinorrhea, and cough—early clinical symptoms largely indistinguishable from other viral respiratory infections. Among individual signs and symptoms of RSV-ALRI, cough has the highest sensitivity for predicting laboratory-confirmed RSV. Hypoxia, wheezing, stridor, nasal flaring, and chest wall

in-drawing can occur during RSV illness, but RSV is difficult to distinguish from other etiologies by clinical examination alone.

The positive predictive value of standard enzyme-linked immunosorbent assay (ELISA) antigen detection is low for common signs and symptoms of ALRI.[35,36] (See the Product section of this report for more information on immune assays). Polymerase chain reaction (PCR) is more sensitive compared to antigen-detection ELISA and allows greater distinction between RSV-ALRI and other ALRI caused by parainfluenza type 3 virus, human metapneumovirus (hMPV), adenoviruses, rhinoviruses, coronaviruses, and influenza viruses that may also produce wheezing (i.e., bronchiolitis). From studies using different diagnostic methods, RSV is associated with the majority of bronchiolitis (31 to 77%), followed by adenoviruses (15 to 31%), hMPV (9 to 11%), parainfluenza viruses (6 to 26%), coronaviruses (0 to 8%), influenza viruses (1 to 23%), and rhinoviruses (0 to 16%).[37–40] Most of these studies are from HICs, underscoring the need to replicate these studies using more accurate diagnostics in LMIC settings. The development and use of more specific diagnostics are also important for establishing accurate vaccine effectiveness estimates. Importantly, current diagnostics do not allow attribution of causality. High bacterial co-infection rates have been reported with RSV-ALRI in LMICs, suggesting possible interactions between causative pathogens of ALRI.[33] Altering other infectious disease patterns may also alter the transmission, or possibly the severity of RSV. The Pneumonia Etiology Research for Child Health (PERCH) studies (conducted in South Africa, Zambia, the Gambia, Kenya, Mali, Thailand, and Bangladesh) have helped to better define viral association with ALRI. They estimate 21.4% of ALRI to be attributable to RSV as adjusted by control data for RSV and other viral relationships relative to ALRI (OR 11.20 [7.21-17.41]).[41]

Transmission, treatment, and severity

RSV is transmitted through large respiratory droplets (10 to 100 nm) by means of close personal contact.[42] RSV can survive on surfaces and can be potentially transmitted by virus contaminated objects or surfaces (fomites). In addition, infection transmission via respiratory droplet occurs when a RSV-infected person touches a second person, who subsequently self-inoculates their mucous membranes with virus acquired from the first individual.[43,44]

Most RSV infections in infants are mild, self-limited, and managed in outpatient settings. Supportive care is the primary therapy, including respiratory support as well as fluid and nutrition management. For more serious cases like bronchiolitis, evidence supporting the use of beta agonists is inconsistent but supplemental oxygen therapy may be required to maintain oxygen saturation at 90% or greater.[45] In addition, fluid supplementation is required in 30% of hospitalized patients with bronchiolitis, with allowance for continued breast feeding in patients with minimal respiratory difficulty.[37,46] Nebulized hypertonic saline given to infants with bronchiolitis increases mucociliary clearance and rehydrates airway surfaces. Although evidence from individual studies of reducing clinical severity in outpatient populations is conflicting, two recent reviews of multiple studies found that 3% nebulized hypertonic saline given to outpatients significantly reduces the hospitalization rate and length of stay.[47] Antibiotics are recommended in patients with bronchiolitis only when specific evidence of coexistent bacterial infection is present.

While much is known about managing RSV disease in newborns and infants, significant uncertainty remains around RSV prevention. What is known is that passive prophylaxis is a safe and effective way of protecting infants at risk for severe RSV-ALRI.[7–9] Palivizumab (Synagis®), a RSV mAb, is the only licensed prophylactic. A 2013 meta-analysis calculated a 51% (36-63%) reduction in RSV hospitalization in infants at high risk for RSV on the basis of prematurity or underlying medical illnesses receiving palivizumab compared to placebo.[10] A gestational age cut off for infants without chronic lung disease (CLD) or congenital heart disease (CHD) has been difficult to define, however, so recommendations for use of palivizumab are limited to high-risk infants.[48] Furthermore, monthly injection requirements throughout the RSV season and palivizumab's high cost reduce its feasibility for LMIC use, necessitating additional options for RSV disease prevention. Strategies for fewer doses, targeted at the highest risk age period have been proposed, but not seriously pursued.

Motavizumab, developed as a more potent derivation of palivizumab, demonstrated non-inferiority to palivizumab among premature and medically high-risk infants. It also underwent testing in healthy full-term infants in HICs deemed high risk for RSV disease on the basis of socioeconomic living conditions similar to what might be expected in LIC or LMIC settings (i.e., the Navajo and White Mountain Apache communities). The product demonstrated a 87% (79-82%) reduction in inpatient medically-attended RSV-ALRI and a 71% (58-80%) reduction in outpatient medically-attended RSV-ALRI in a randomized, placebo-controlled trial of healthy full term infants. Motavizumab, however, was not licensed for clinical use due, in part, to a reported excess of rashes in clinical trial subjects where motavizumab was compared to palivizumab.[49] Additional options for RSV prevention are needed.

Although the association between RSV bronchiolitis and consequent asthma is widely reported in HICs, little information is available from LMICs.[50] This evidence comes from observational studies and, as such, cannot evaluate causality, which requires intervention studies. Understanding whether early RSV-ALRI causes subsequent asthma or exacerbates an underlying predisposition to wheezing could contribute to the value proposition for RSV prevention.[51] Data from several studies in which palivizumab or motavizumab significantly prevented early RSV ALRI suggest RSV mAb may reduce incidence of wheezing illness in the short-term, and two reports demonstrated no change in wheezing outcomes over the longer term.[49, 52–55] Differences across studies such as gestational age of study populations, endpoints, and study power for assessing outcomes may confound the interpretation of results. Development of methods for generating robust data to assess the effect of RSV prevention on subsequent wheeze/asthma is needed.

Finally, to better measure effect and establish demand for maternal RSV vaccines, the ability to diagnose bronchiolitis and ALRI caused by RSV in LMICs is important. This knowledge will be critical for calculating RSV-attributable rate reductions in trials of maternal RSV vaccines against severe ALRI and will need RSV-specific diagnostics. Also needed are studies to measure an attributable effect and duration of effect due to RSV MI on bronchiolitis and wheezing illness in infants and children, measured by long-term follow up of clinical trial participants. Narrow band age stratification will also be needed to assess the effect of waning maternal antibody as the infant cohort ages.

Disease burden

This section covers the global epidemiology of RSV including morbidity, mortality, and risk factors associated with infection, disease, and severity of disease. Findings are a result of a systematic literature review and specific methods for searches are available upon request. Though focused mainly on infants, the analysis gives attention to RSV in pregnant women as well.

Existing and missing evidence or conditions on the ground

Historically, most RSV epidemiologic data come from HICs; however, the evidence on RSV epidemiology for LMICs has been growing.[4,33] The Global Burden of Disease Study in 2015 estimated population-attributable fractions for disease incidence and mortality for pneumococcus, *Haemophilus influenzae* type b, influenza, and RSV in children younger than five years of age. RSV accounted for an estimated 15.4% of incident lower respiratory infection

KEY HIGHLIGHTS: RSV DISEASE BURDEN

Progress

- WHO is piloting RSV surveillance in 14 countries through the GISRS, to provide evidence of RSV disease burden, seasonality, and risk factors in many geographical regions, including LICs.
- The Novavax Ph3 trial will provide some age-stratified disease data, though more will be needed, particularly from populations with co-morbidities.

Work remaining

- RSV disease characterization by narrow band age strata in infants is needed to assess the value of a maternal RSV vaccine once its duration of protection is known.
- RSV disease assessment requires appropriate diagnostic capacity at hospital and community levels before and after vaccine introduction to provide burden awareness and demonstrate vaccine effectiveness.

(15,677,200 cases in 195 countries with 36,363 deaths due to RSV).[56] Another recent global disease burden study modeled data from 329 studies of laboratory-diagnosed RSV-ALRI, stratifying by age within the first five years of life. Approximately 0 to 6% of these studies were in LICs, depending on the parameters under consideration.[5] For 2015, the model estimated that 33.1 million (uncertainty range 21.6-50.3) episodes of RSV-ALRI occurred globally in children younger than five years of age—an estimated 30.5 million (uncertainty range 19.5-47.9) of which occurred in LMICs. Of those, approximately 10 million (33%) were in children less than one year of age.[57] India, China, Nigeria, Pakistan, and Indonesia accounted for 50% of RSV-ALRI, as expected given the large populations in these countries. The model estimated that 3.2 million (uncertainty range 2.7-3.8) hospital admissions occur for RSV-ALRI in children younger than five years of age globally. Of these, 1.4 million (45%) (uncertainty range 1.2-1.7) were in infants less than six months of age. About 2.6 million (uncertainty range 2.2-3.1) hospitalized RSV-ALRI cases came from LMICs. Age-stratified incidence per 1,000 children among these LMIC hospitalizations was above 20 for the first year of life and diminished to 1.0 from 24 to 50 months of age (see Figure 2). Though nearly half of the severe RSV disease occurred in the first six months of life, these data also revealed substantial disease remaining after the first six months of life.

Globally, an estimated 118,200 (uncertainly range 94,600-149,400) in-hospital deaths are attributable to RSV-ALRI among children less than five years of age.[5] Of these, 45% occur in infants less than six months of age and 99% are in LMICs. Despite the lower RSV-ALRI hospitalization rate in LICs, high mortality occurs in those hospitalized, especially in children six to 11 months of age (Figures 2 and 3). A marked increase in the incidence of severe RSV-ALRI or mortality may indicate when an infant's maternal antibodies decline and are no longer protective. Among hospitalized RSV-ALRI cases, the median age of death is five months of age in LMICs and seven months of age in HICs.[5] Unfortunately, these age-stratified estimates in LICs are imprecise and insufficient for predicting duration of transplacental antibody in infants (see Figure 2). Additional age-stratified incidence and mortality data will be needed in LICs before initiating observational studies to measure the effect of RSV MI on the protective duration of transplacentally-acquired RSV antibody in infants. Ideally, those data will be gathered before vaccine introduction so that a meaningful comparison can be conducted to assess impact post-introduction. The ongoing Novavax Ph3 trial of a leading maternal RSV vaccine candidate may provide some of these data. The trial does not include LIC sites or participants with co-morbidities, so additional data will likely be needed to inform decision-making.[15] The Child Health and Mortality Prevention Surveillance project is designed to assess causes of global mortality in children under five years of age and may contribute to filling this gap; however, age stratification by narrow bands of one to three months in infancy will be needed.[58]

Disease data are still insufficient from LICs where available data are gathered mostly in hospitals, to which patients in rural areas have limited access. This lack of data is likely to impede the ability to monitor impact and assess the value to very poor countries of making an investment in RSV MI. WHO's 2017/2018 initiation of a RSV surveillance pilot using the Global Influenza Surveillance and Response System (GISRS) in 14 countries representing the WHO geographic regions will begin to address this challenge. Though the program encourages ambulatory surveillance in the community where resources allow, the current system is not narrow band age-stratified and has a primary focus on data from sentinel hospitals.[59]

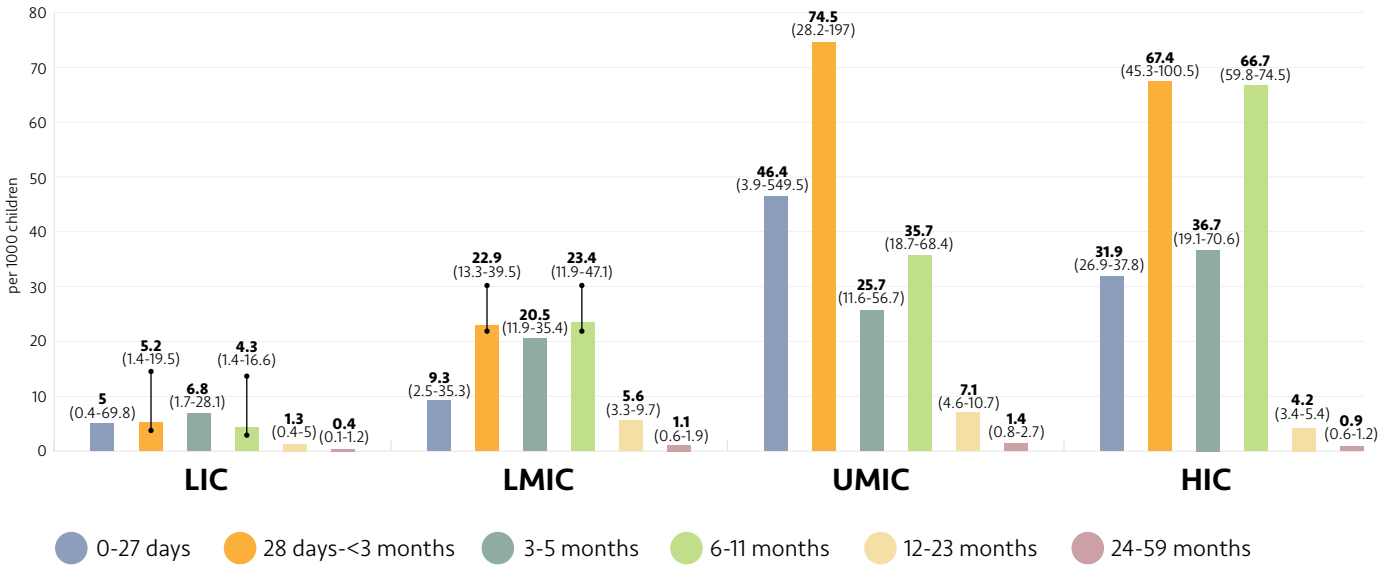
RSV risk factors

While risk of RSV infection is related to factors such as formula-feeding and household crowding, the primary focus here is on risk factors for severe RSV-ALRI.[60] Prematurity is one of the most important risk factors for severe RSV-ALRI. In a systematic review that includes data from two LMICs and four HICs, the global hospitalization rate of RSV-ALRI is 63.9 per 1,000 children per year among premature infant live births. This is three times greater than full-term infants (19.2/1,000) and 16 times greater than in children younger than five years of age who were not premature (4.4/1,000). The two LMICs, Brazil and Peru, have rates of 99.0 and 116.2 per 1,000 children per year for preterm infants, respectively. Case fatality rates (CFR) in premature infants are similarly much higher in these countries (33.3 and 27.8, respectively per 1,000 premature infants per year) when compared to HICs with rates of 1 per 1,000 premature infants per year.[61] A review of prematurity and associated mortality globally finds 60% of the 15 million global annual premature births occur in ten countries, nine of which are LMICs. If these findings are extrapolated to the disproportionate CFR for RSV-infected preterm infants in the two aforementioned LMICs, the impact of undiagnosed RSV in premature infants could be substantial in LMICs.[61]

CLD, often resulting from prematurity, is also a risk factor for RSV severity in infants. Most data on this are from HICs where CLD has declined 47% since 1997, partly due to the use of lung surfactant administered to premature newborns in HICs since the 1990s.[62] The attributable fraction of severe RSV in association with CLD would also decrease. Surfactant has been used less widely in LMICs, thought to be partly due to inconsistent administration that yields less evidence of effectiveness.[63,64] Similarly, CHD in children poses increased risk for RSV hospitalization but has declined as a risk factor by 50% since 1997.[65] Data on CHD and CLD as risk factors for RSV severity are largely missing from LMICs. Finally, HIV appears to be a risk factor for severe RSV based on two studies from Africa. The studies, conducted in South Africa and Mozambique, reported risk ratios for RSV hospitalization of 3.1 to 5.6 and 2.2 to 6.5, respectively, compared to RSV hospitalization in non-HIV infected infants of the same ages.[66,67] Another study from South Africa demonstrated a 31.1 (5.4-179.8) odds ratio of death for severe RSV in HIV- infected persons.[68]

Other risk factors for RSV disease severity have been examined with mixed findings. Malnutrition, for one, is a risk factor according to studies in LMICs.[33,69,70] Overall, more data are needed on the effect of degree of malnutrition on RSV severity. In addition, whether or not co-infection, other causes of ALRI, or malaria are risks for RSV severity is unclear.[67,71–81] Although data are insufficient on the effect of co-infection on RSV severity, additional information may become available from the aforementioned combined RSV and influenza surveillance efforts by WHO.[59]

FIGURE 2. **Estimated RSV-ALRI hospitalization rates by narrow age bands, 2015**

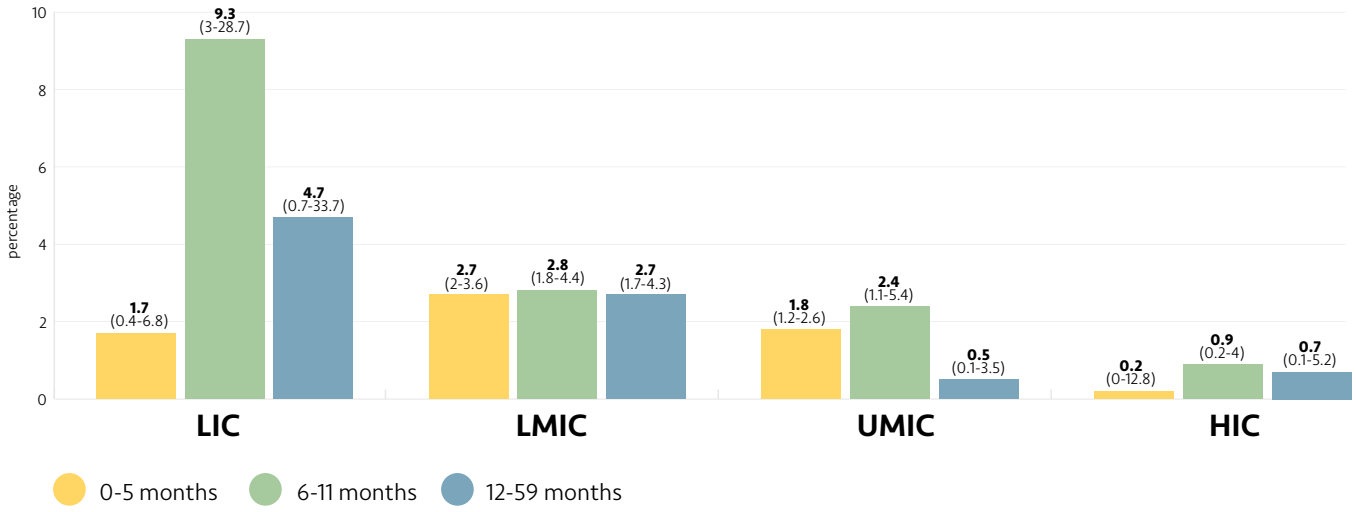


Source: Shi et al, *Lancet* (2017)

LIC = low-income country (3 to 5 studies); LMIC = lower-middle-income country (9 to 17 studies); UMIC = upper middle income country (5 to 15 studies)

HIC = high-income country (9 to 34 studies)

FIGURE 3. **Estimated percent fatality of RSV-ALRI hospitalizations by narrow age bands, 2015**



Source: Shi et al, *Lancet* (2017)

LIC = low-income country (9 studies); LMIC = lower-middle-income country (16 studies); UMIC = upper-middle-income country (12 studies)

HIC = high-income country (6 studies)

Figures 2 and 3 explained:

- Figure 2 indicates relatively low severe RSV in infants zero to five months old, especially in LICs. This is in part a function of low hospital attendance for severe RSV cases in LICs and few studies in these settings (approximately 6% of studies).[5]
- Figure 3 indicates high-case fatality rates in LICs in infants zero to five months of age but wide confidence intervals. This is partially a function of the paucity of studies and small samples sizes involved in LIC settings.
- These two figures indicate the gap in RSV disease burden data in LICs and the importance of community-level surveillance using appropriate diagnostics in addition to hospital-based surveillance.

Vaccine effect on mothers

Although MI with maternal RSV vaccines is primarily intended to protect infants, direct benefits may occur for the mother as well. RSV infection in pregnant women may typically be associated with asymptomatic or mild disease, but reports of severe disease cases and adverse outcomes exist such as fever, respiratory distress, preterm labor, and hospitalization, including intubation in this population.[82,83] Given the very small numbers in these studies, no statistical comparison with the non-RSV infected population of pregnant women is possible and further studies could help determine the relevance of these finding. Also possible is that MI prolongs post-partum immunity in the mother, thereby reducing potential infection of the mother and possible transmission to her infant. This potential is being assessed in the leading maternal RSV vaccine candidate Ph3 trial.

Seasonality

RSV seasonality is an important consideration when discussing MI due to the variable exposure of infants in their first year and the protection offered by waxing and waning maternal RSV antibody titers due to periodic natural infection. Maternal antibodies and associated cord blood titers vary seasonally, likely due to boosting maternal RSV antibody during the RSV season.[84,85] Data on the impact of regional RSV seasonality on RSV severity are insufficient and conflicting.

Five systematic reviews assess RSV seasonality and 60% of current studies are from HICs.[34] These studies generally reflect seasonal patterns in temperate zones.[33,86–89] Most studies do not describe mortality or disease severity by seasonality. A 2018 global overview of RSV seasonality compares regional variations using national surveillance systems in 27 countries, though most are also in HICs.[90] Studies examining seasonality in LMICs are often single-hospital or short-term with a small sample size of RSV cases.[33,86–89] The WHO RSV surveillance pilot, which began in 2017/2018, will add RSV surveillance to the influenza surveillance platform and gather seasonality data in 14 countries, including 8 LMICs: Brazil, Cote d'Ivoire, Egypt, India, Mongolia, Mozambique, South Africa, and Thailand.[59]

Based on available data, general worldwide patterns of RSV seasonality emerge. In the temperate regions of the northern and southern hemispheres, RSV peaks in the winter months (December to March and May to September, respectively), though outliers occur and differ across years. In tropical zones, RSV peak timing is inconsistent and some countries experience semi-annual peaks. Across all regions, the median duration of epidemics is three to five months.[86] Substantial intra-country variation occurs over large geographical areas or areas with wide variations in regional climates (e.g., Brazil, Australia, and the United States). Note that diagnostic modality may influence the interpretation of seasonality. This scenario was recently described through the use of more sensitive PCR testing for RSV that resulted in apparent seasonal shifts compared with data derived from antigen detection testing alone.[91]

Despite studies demonstrating seasonal trends, even in the tropics, annual seasonal variation in RSV occurrence, the possibility of RSV outside the typical season, and the length of pregnancy may make immunizing selectively in anticipation of seasonal RSV outbreaks unfeasible in LMICs. More data on seasonality from LMICs are needed to inform appropriate approaches for programmatic implementation and to verify current assumptions driving vaccine impact models and the vaccine value proposition.

RSV transmission

Community-based studies of RSV transmission dynamics in both LMIC and HIC settings suggest that both in- and out-of-home transmission occur with out-of-home contact between schoolchildren often bringing the infection into the household. Younger children are the most frequent transmission vectors due to their greater likelihood of being symptomatic, having higher viral loads, and shedding longer. Furthermore, the median age of first infection is one year of age or less and the vast majority of children experience a primary RSV infection by their third birthdays. Immunity to reinfection appears temporary and reinfections are common.[92–95] Studies of RSV in Alaskan Natives in a situation similar to LMICs identify a lack of plumbing and household crowding as significant risks for acquiring severe RSV disease.[96] Not all studies support this finding. A 2012 systematic review identifying 11 studies evaluating residential crowding and severe RSV disease finds a mix of results depending on the study design and definition of crowding.[97] More data on transmission dynamics within households and communities are needed to predict RSV MI's relative effectiveness as a strategy for protecting infants from severe RSV disease, particularly if prevention of RSV in pregnant women contributes to herd immunity.

RSV surveillance and diagnostics

As mentioned earlier, improved disease surveillance is needed in lower-middle income countries and LICs in particular. Although sentinel sites gather disease data in LICs, risk factors such as prematurity, CHD, CLD, co-morbid conditions, and seasonality are difficult to accurately measure due to the relatively few cases identified resulting from too few sentinel surveillance sites in these settings. While LMICs exhibit different

patterns than HICs, highly systematic studies are available from indigenous communities in the United States and Canada that may be useful in extrapolating to somewhat similar circumstances within LMICs.[96]

A major gap in this area is a critical lack of diagnostic capacity in LICs. Without adequate diagnostics, ALRI surveillance cannot distinguish RSV from other causes of ALRI. For example, RSV surveillance studies of hospital and non-urban settings in Kilifi, Kenya, document that only a quarter of severe RSV is seen at a hospital.[98] This finding suggests the need for enhanced diagnostic capacity and disease surveillance outside hospital settings to fully understand the potential impact of a maternal RSV vaccine. The relative lack of diagnostic capacity impinges on the ability to gather age-stratified disease data from LICs and community-based health centers for ages at high risk for severe disease to justify the need for maternal RSV vaccine introduction.

Major disease gaps distilled

RSV clinical disease and disease burden are well described to support advancing suitable maternal RSV vaccine candidates. Most of the gaps listed in Table 2 represent information that would be helpful and important in fostering vaccine introduction globally but would not preclude suitable vaccine candidates from moving forward toward licensure.

TABLE 2: Disease—tiered gaps in evidence or conditions on the ground

Essential and specific to maternal immunization[a]
• Evidence of maternal RSV vaccine effect against severe RSV disease in infants. • 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 LMICs. Limited data currently available in publication and in gray literature should be consolidated and disseminated.
Essential across immunizations[b]
• Improved capability for detecting RSV in LMICs in both hospital settings and non-urban settings where hospital access is lacking, which is needed to inform country demand and introduction decisions based on disease burden and for monitoring vaccine effect after introduction.
Non-essential but supportive[c]
• Evidence of maternal RSV vaccine effect against RSV infection in infants. • Disease models to predict the effectiveness of maternal RSV vaccines. Data on the level and duration of vaccine-induced and naturally-derived maternal RSV antibody can be used to model the relationship between maternal RSV antibody levels in serum and breast milk and duration of protection from RSV disease and infection in infants' first few months of life. • Additional evidence on RSV burden in pregnant women. • Additional evidence from LMICs on RSV seasonal variation, annual variation in disease incidence, transmission dynamics, RSV serogroup prevalence, and clinical treatment and management availability and standards. • Evidence on effect of pneumococcal and influenza immunizations on RSV disease patterns, including the proportion of bronchiolitis and other ALRIs attributed to RSV.

[a]A gap in information or conditions that is unique to MI and that must be addressed for MI decision-making and/or introduction to move forward
[b]A gap in information or conditions that is generally applicable across vaccines and that must be addressed for MI decision-making and/or introduction to move forward
[c]A gap in information or conditions that, if addressed, could strengthen or accelerate MI decision-making and/or introduction, but is not required to move forward

9.2 PRODUCT

Since 2013, product development for RSV prevention has surged. Forty vaccines and four mAbs are in development, 19 of which are in clinical trials.[2,14] (Appendix 5 contains a comprehensive list of the product candidates and their status as of May 2018.) Several candidate interventions target preventing severe RSV disease in infants and children. Two late-stage candidates focus on protecting infants in their first months of life. One uses active immunization of the mother during pregnancy to provide passive protection to her infant via maternal antibody. The other uses immunoprophylaxis of infants with a mAb. Both approaches provide neutralizing antibody specific for the RSV fusion (F) protein to protect infants, though maternal antibody is polyclonal and the mAb is not. This section summarizes information on key product and immunization parameters that will affect decision-making around vaccine use in LMICs. It also provides an overview of anticipated vaccine availability, program suitability, and supply.

Options for disease prevention

The vaccine candidate developed by Novavax is designed for MI to boost pre-existing RSV antibody responses in pregnant women, which are then naturally transferred via the placenta and, possibly also via breast milk, to their infants. A Ph3 multi-country clinical trial began in December 2015 to evaluate the vaccine candidate in healthy pregnant women and their offspring.[15] As of March 2018, the program is in the third season of enrollment and includes 87 sites in 11 countries, including six high income (United States, United Kingdom, Spain, Australia, New Zealand, and Chile) and five middle income (Argentina, Bangladesh, Mexico, Philippines, and South Africa). The product candidate has US Food and Drug Administration (FDA) Fast Track designation, which may accelerate the time to US licensure.

The lead mAb candidate is being developed by MedImmune, LLC/Sanofi Pasteur. It is designed to mitigate the monthly dosing and high product cost barriers that make palivizumab use infeasible in many LMICs. Like palivizumab, the mAb candidate is administered intramuscularly, but the development strategy currently seeks an indication for single-dose administration to all infants entering their first RSV season. This lead mAb candidate is currently being tested in a Phase 2b trial of 1,500 preterm infants in 161 sites across the United States, Canada, United Kingdom, Europe, South America, Australia, and South Africa.[99] The study is estimated to conclude in December 2018 and a subsequent Ph3 trial in healthy full-term infants is planned. In March 2017, Sanofi Pasteur and MedImmune announced a development and commercialization partnership.[100] The product candidate also has FDA Fast Track designation, which may accelerate the time to US licensure.

Vaccine and immunization characteristics

A maternal RSV vaccine candidate is now in late-stage clinical development and licensure for such a vaccine could be groundbreaking on multiple fronts. It could be the first licensed RSV vaccine *and* the first vaccine developed specifically for administration to pregnant women to protect their infants. That indication will be important for allowing rapid adoption of the vaccine in MI programs. This section describes WHO guidance, available information, and gaps around vaccine and immune parameters as they relate to immunization programs in LMICs. The evidence needs for immune assays to facilitate the comparison of immune responses to candidate RSV vaccines are also summarized.

KEY HIGHLIGHTS: RSV VACCINE AND IMMUNIZATION CHARACTERISTICS

Progress

- Multiple products are in development to prevent RSV disease in young infants.
- The WHO RSV PPC guidance helps ensure that emerging vaccines are suitable for use in LMICs. The leading maternal RSV vaccine candidate aligns with many of these parameters.
- A Ph3 trial is in progress to provide data on safety and efficacy of a maternal RSV vaccine.
- Antiserum to the Respiratory Syncytial Virus WHO 1st International Standard is now available to harmonize RSV neutralization assay data across vaccine candidates.

Work remaining

- Data are needed to understand the impact of maternal and infant co-morbidities on RSV vaccine immunogenicity, maternal antibody transfer, and vaccine safety.
- Data are needed from LMICs on the impact of co-administration of maternal RSV vaccine with other vaccines.

Existing and missing evidence or conditions on the ground

Enhanced respiratory disease

RSV vaccine development was hampered in the mid-1960s after clinical trials testing a formalin-inactivated whole virus RSV vaccine (FI-RSV) in pediatric populations resulted in enhanced respiratory disease (ERD) upon subsequent RSV infection.[101–104] The effect was seen in the youngest children (who were likely RSV naïve). The exact immunological mechanisms are still not completely understood to this day.[105] Studies of ERD in animal models show that passive transfer of FI-RSV-induced antibody does not result in ERD.[106] The success of RSV immunoprophylaxis with palivizumab demonstrates that antibodies can protect against severe RSV disease.[10]

Maternal antibody transfer

Starting in childhood and continuing through adulthood, multiple infections with RSV over time are common. Therefore, pregnant women have pre-existing RSV-specific maternal antibody that is naturally transferred to the infant via the placenta as immunoglobulin G (IgG) and breast milk as secretory IgA. Maternal RSV neutralizing antibody titers have been shown to correlate with protection from RSV infection and hospitalization in the infant.[11–13] Studies also indicate that breastfeeding reduces the severity of RSV illness in early infancy.[107,108] Increased levels of both maternal IgG and IgA antibodies have been described after vaccination during pregnancy.[109–112] These findings support a rationale for vaccination in pregnancy to boost maternal RSV antibody, which is naturally transferred to the fetus and confers protection in the infant's first months of life.

Transplacental maternal antibody transfer is mediated though the neonatal Fc receptor, a protein found on placental cell surfaces with specific binding for the Fc (Fragment, crystallizable) antibody constant region. Transfer increases throughout pregnancy, most significantly in the third trimester.[113] IgG is differentially transferred across the placenta, and the active transport mechanism frequently leads to higher antibody concentrations in a full-term infant compared to the mother.[114] Several factors reduce maternal antibody transfer including maternal HIV infection, malaria, hypergammaglobulinemia, and malnutrition.[114–116] Evidence shows that babies born preterm or with low birth weight also have lower levels of maternal antibodies at birth.[115,117]

Maternal RSV vaccine and immune characteristics

In consultation with vaccine developers and experts, WHO developed several resources to inform RSV vaccine development. To facilitate outcome comparison across clinical studies, in 2015 WHO proposed case definitions that include disease severity criteria for RSV-ALRI to be used by developers.[118] Collection of standardized data, including continuous variables, will allow comparison across studies regardless of case definition. The WHO Preferred Product Characteristics (PPC) for RSV vaccines was published in 2017 to provide guidance on product parameters that have a direct operational impact on immunization programs and includes discrete guidance for maternal vaccine approaches.[119] No RSV vaccine is licensed yet, so key parameters and alignment based on available information for the leading maternal RSV vaccine are described in this section, with areas called out where additional data are needed.

The WHO PPC states a preference for maternal RSV vaccines that can be administered over the second or third trimester of pregnancy and requires only one dose to maximize logistical possibilities for delivery as part of antenatal care (ANC) in LMICs. The lead maternal RSV vaccine candidate uses a single-dose strategy, and the Ph3 trial targets a third trimester immunization window of 28 to 36 weeks of gestation.[15] The timing of immunization in pregnancy may affect vaccine efficacy in infants born preterm. The ability to immunize women early in the third trimester (or sooner) may enhance outcomes in this population. Data assessing whether the immunization window could be broadened would facilitate vaccine delivery in regions where precise assessment of gestational age is challenging and where ANC coverage during the second and third trimesters is low.[120]

The WHO PPC preference is for maternal vaccines that can be administered to all pregnant women since excluding women with co-morbid conditions and identifying high risk pregnancies in LMICs will be challenging. As the lead maternal RSV vaccine candidate Ph3 trial is restricted to healthy, low-risk pregnant women, more data are needed to understand the effect of maternal co-morbidities and preterm delivery on RSV vaccine immunogenicity and maternal antibody transfer. Data are also needed on the effectiveness of repeat vaccination across multiple pregnancies.

The WHO PPC calls for the RSV vaccine to have a safety profile similar to vaccines currently recommended for use during pregnancy (i.e., influenza, tetanus toxoid (TT), and acellular pertussis), and no indication of ERD in the offspring. Initial study results of the Novavax maternal RSV vaccine candidate indicate no evidence of vaccine-induced ERD in the mother or the infant, no vaccine related severe adverse events (SAEs), and no significant imbalance of SAEs or unsolicited adverse events (AEs).[121] Additional data on adverse events following immunization (AEFI) will be available after completion of the Ph3 trial.[15] Post-marketing studies are needed

to further evaluate RSV vaccine safety and AEFI in pregnant women and their infants, including those with co-morbidities. These studies will be critical for collecting data on safety signals and may also provide data on potential risk factors for AEFI such as co-morbidities or pre-existing medical conditions.[122] Identifying differences in both common and rare safety outcomes will require following a larger cohort. Additionally, more data on background rates of maternal and neonatal AEs are critical to interpret safety signals.

The WHO PPC preference is for a maternal RSV vaccine that has greater than 70% efficacy against confirmed severe RSV disease in children from birth to four months of age. The Ph3 trial of the lead maternal RSV vaccine candidate will assess confirmed RSV-ALRI in infants through 90 days of life. If successful, additional analyses will be performed to assess the duration of protection.[15] A December 2017 informational analysis indicated efficacy in infants at 90 days to be greater than 42%.[123] The Ph3 trial is intended to provide the immunogenicity, safety, and efficacy data needed to support licensure/marketing approval for the maternal RSV vaccine. While the trial will provide data on the vaccine in healthy populations, additional studies are needed to understand the effect of maternal and infant co-morbidities on RSV vaccine efficacy and effectiveness.

Interactions between vaccines can occur through several mechanisms and can result in inhibition or enhancement of immunogenicity.[124] Existing maternal influenza and pertussis vaccines are co-administered without safety issues and multiple childhood vaccines are co-administered without a demonstrated reduction in effectiveness.[125] The WHO PPC calls for immunologic non-interference of RSV vaccine to be demonstrated upon co-administration with other vaccines recommended for use in pregnancy. Data are specifically needed to assess the impact of maternal RSV vaccine co-administration with other maternal vaccines used in LMICs, with tetanus vaccine as a priority.

Immune assays

The 2017 WHO RSV Vaccine Research and Development Technology Roadmap called for development of quality assured standard reference immune assays to facilitate the comparison of immune responses to candidate RSV vaccines.[126] The most commonly used assays to measure RSV humoral immunity are based on *in vitro* neutralization. While some studies have determined relative correlates of protection based on neutralizing antibody, no agreement has been achieved on a standardized assay or protective antibody titer.[127,128] Progress in this area includes the Antiserum to Respiratory Syncytial Virus WHO 1st International Standard, established for harmonization of neutralization assay data generated using RSV A virus strains. The ability to harmonize data across RSV B virus strains is currently being assessed. The reference standard facilitates comparison of neutralizing antibody responses across vaccine candidates and is available through the UK's National Institute for Biological Standards and Control.[16] High neutralizing antibody titers are associated with a reduced risk of RSV infection; however, infections are still observed in individuals with high titers.[16] Therefore, alternate assays are also being used to assess RSV antibody responses, but lack of standardization or harmonization of alternative assays prevents comparison of results across studies and vaccine candidates. Efficacy studies may provide evidence to establish an antibody correlate of protection applicable to maternal, umbilical cord, and/or infant blood for similar maternal RSV vaccines.

Vaccine availability, program suitability, and supply

This section summarizes anticipated timing for the lead RSV prevention products becoming available for introduction. The anticipated maternal RSV vaccine suitability for use in LMICs, and manufacturer ability to meet supply demands are also discussed.

KEY HIGHLIGHTS: RSV VACCINE AVAILABILITY, PROGRAM SUITABILITY, AND SUPPLY

Progress

- Comprehensive WHO guidance is available related to vaccine program suitability and supply.
- The Gavi 2018 VIS is considering investment in RSV vaccines.
- The lead maternal RSV vaccine candidate could reach licensure by late 2020 or early 2021, with first LMIC introductions to follow as early as 2023.

Work remaining

- A vaccine supply strategy is needed to inform planning for introductions in LMICs.

Existing and missing evidence or conditions on the ground

Multiple RSV prevention products are in development, including vaccines for MI, mAbs for administration to infants at birth, and pediatric vaccines.[2] The two

interventions expected to be available first are a maternal RSV vaccine from Novavax and a RSV mAb from MedImmune/Sanofi Pasteur. Both are in late stages of development with the maternal RSV vaccine candidate expected to be licensed first (2020/2021 estimate), followed by the mAb (2022/2023 estimate).[15,99,123]

Availability of products in LMICs is largely dependent on WHO prequalification (PQ), which occurs after the first licensure. WHO PQ aims to ensure that diagnostics, medicines, vaccines, and immunization-related equipment and devices for high-burden diseases meet global standards of quality, safety, and efficacy. The PQ process consists of a transparent, scientifically sound assessment that includes dossier review, consistency testing or performance evaluation, and site visits to manufacturers. The United Nations (UN) and other UN-associated procurement agencies use this information and other procurement criteria, to make purchasing decisions regarding diagnostics, medicines, and/or vaccines.[129-131]

One component of the PQ evaluation process is programmatic suitability.[130] Due to the advanced development stage of the lead maternal RSV vaccine candidate, most product characteristics are already fixed for the near term and appear to align with both the WHO PPC for RSV vaccine and other programmatically suitable vaccines.[119,130] The only unique characteristic that may affect the feasibility of administration is the timing of vaccination in pregnancy, since determining precise gestational age is challenging in many LMICs and often ANC coverage during the second and third trimesters is low.

Based on the estimated timeframes required for licensure, WHO PQ, funding decisions, and implementation readiness, the first introductions and large-scale use of the lead maternal vaccine candidate in LMICs could occur as early as 2023/2024. Greater precision around the timing of RSV intervention licensure and PQ will improve the ability to reliably predict when the intervention(s) will be available in LMICs. The timing of the first licensure of the vaccine is largely dependent on the results of an interim analysis, expected to be available in late 2018 or early 2019. Funding support for RSV vaccine and delivery programs will need to be identified for LMICs to enable planning and timing for vaccine introduction. Some of these countries are eligible for funding from Gavi, the Vaccine Alliance. Every five years Gavi runs a Vaccine Investment Strategy (VIS) to scan the horizon for potential investments in vaccines that are licensed or are in late stages of development with reasonable expectations of licensure. The vaccines are compared using an analytical approach including assumptions regarding future vaccine price and a recommendation for use by SAGE/WHO. The VIS decisions inform the funding amounts Gavi must raise to support implementation without delays. In the case where vaccine licensure is in the future, Gavi conducts a short final confirmation that the vaccine will be funded once it has been prequalified by WHO and prior to offering countries the opportunity to apply for the vaccine. The Gavi VIS funding decision for RSV will be known in late 2018. Following these outcomes, predicting introduction timing more precisely will be possible.

A well-informed vaccine supply strategy will be pivotal in achieving widespread licensure and availability in LMICs. Global stakeholders, including Gavi, WHO, the Bill & Melinda Gates Foundation, the United Nations Children's Fund (UNICEF), and organizations like PATH will need to guide the manufacturer in demand and timing projections to plan for sustainable vaccine supply. Better projections will be known after late 2018 since a decision by Gavi to fund the maternal RSV vaccine through its VIS is likely to increase demand. The use of RSV interventions in middle-income countries that are not Gavi-eligible would also benefit from a structured approach to demand forecasting, introduction planning, and information flows. Novavax has relationships with global immunization stakeholders and has an agreement with the Gates Foundation that allows the company access to information necessary to plan for a sufficient and sustainable supply of its vaccine, should it be licensed and prequalified by WHO. Delays in licensure, PQ, and supply caused by technical challenges exist and are risks for any manufacturer including Novavax, particularly since the RSV vaccine candidate would be their first to be licensed and commercially produced. Common for this development stage, no evidence is currently available to indicate that the manufacturer will fail to have the capacity to supply a sufficient quantity of maternal RSV vaccine for LMICs. Any delays in completing the PQ process, funding, and demand clarity could increase the risk of delayed introductions in LMICs.

Major product gaps distilled

As a result of the advanced development stage for the lead maternal RSV vaccine, several of its product parameters are already known and appear suitable for a MI program. Key gaps remain, however, to maximize rapid launch and uptake in LMICs. Several of the information needs and gaps identified in Table 3 are essential to maternal RSV vaccine decision-making, introduction, delivery, and/or uptake. Some of them are specific to MI due to the unique target population of the vaccine, while others are applicable across all vaccines or may not be essential to moving the vaccine forward but could accelerate progress.

TABLE 3: **Product—tiered gaps in evidence or conditions on the ground**

Essential and specific to maternal immunization[a]

- Immunogenicity, safety, and efficacy data to support licensure and marketing approval of a maternal RSV vaccine. Data collected should include duration of infant protection.
- Additional data on the effect of maternal co-morbidities and preterm delivery on RSV vaccine immunogenicity, maternal antibody transfer, and vaccine effectiveness.
- 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.
- Post-marketing studies and routine surveillance to further evaluate RSV vaccine safety and document AEFIs in pregnant women and their infants in LMICs, including those with co-morbidities.
- Additional vaccine effectiveness, immune, and safety data to inform the potential for broadening the RSV vaccination window beyond that used in the Ph3 trial, particularly for regions where assessing gestational age is challenging and where ANC coverage during the second and third trimesters of pregnancy is low.

Essential across immunizations[b]

- Collection of standardized data, including continuous variables, to allow comparison across studies regardless of case definition.
- Background rates on pregnancy outcomes in LMICs to facilitate maternal RSV vaccine safety data interpretation.
- Greater precision around the timing of RSV intervention licensure and WHO PQ to improve estimates of intervention availability in LMICs.
- Funding support for RSV vaccine and MI delivery programs identified for Gavi-eligible and non-eligible LMICs to enable development of plans and timing for vaccine introduction.
- 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.
- No WHO prequalified maternal RSV vaccine currently exists. .

Non-essential but supportive[c]

- 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.
- 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.
- Standardized immune assays or harmonized assay data using appropriate international reference standards to allow comparison across studies and vaccine candidates.
- When pediatric RSV vaccines become available, evaluation of interference of vaccine-induced maternal RSV antibody on active immunization of infants against RSV.

[a]A gap in information or conditions that is unique to MI and that must be addressed for MI decision-making and/or introduction to move forward
[b]A gap in information or conditions that is generally applicable across vaccines and that must be addressed for MI decision-making and/or introduction to move forward
[c]A gap in information or conditions that, if addressed, could strengthen or accelerate MI decision-making and/or introduction, but is not required to move forward

9.3 HEALTH ECONOMICS AND FINANCING

Health economics and financing information are critical evidence components needed for global and country decision-making and implementation planning for RSV MI. Health economics evidence helps ensure that prioritized interventions are impactful, affordable, an efficient use of resources, and can be financially sustained over time. Health economists and other stakeholders assess and analyze the cost of illness associated with a disease and collect the costs of an intervention and its delivery strategy. These economic data are often combined with information on disease burden and the attributes of an intervention to estimate the health impact, cost-effectiveness, and total cost of scaling up new and underutilized interventions. Finally, understanding the costs of an intervention allows stakeholders to estimate the required budget and identify potential sources of financing. This section applies these health economics and financing needs to RSV disease and potential immunization interventions.

Cost of illness

Cost-of-illness data (sometimes referred to as the economic burden of disease) detail the resources expended to treat a health condition. If an intervention is available and implemented, then some of these costs may be averted. Cost-of-illness data include costs incurred by a variety of groups including households, the health system, and society. These costs include resources used to pay for medical care (direct medical costs), additional expenses such as transportation (non-medical direct costs), and productivity costs due to missed work (indirect costs). These cost categories help form a comprehensive picture of the resources associated with a health condition. In addition, health economists often seek to understand who pays these costs to help determine distributional considerations or broader economic consequences of disease such as expenses that push a household into poverty.

KEY TAKEAWAYS ON COST OF RSV ILLNESS

Progress

- A RSV cost-of-illness study in Malawi, a LIC, and future studies in other countries will provide additional data on the cost of RSV illness.
- Cost-of-illness data are available for other respiratory infections and are likely to be informative for RSV.

Work remaining

- Additional data are needed on cost of RSV disease in LMICs, including cost of treatment and sequelae, particularly in regions without studies.
- Cost similarities between RSV and other illnesses need to be demonstrated.

PATH/Gabe Bienczycki

Existing and missing evidence or conditions on the ground

Information on the costs associated with RSV disease in infants and young children is insufficient. No information is available on the cost of RSV illness in pregnant women, though the importance of this information is uncertain given the limited evidence that RSV affects pregnant women.[82,83] The AMI health economics and financing WG identified six RSV cost-of-illness studies (China: 3, Malaysia: 1, Bangladesh: 1, and Jordan: 1) focused on infants and children in LMICs with costs of inpatient care ranging from US$104 in Bangladesh to $662 in China. [132–137] All but one of the studies assess costs in Asia and no published studies examine costs in Africa or Latin America. The WG did not identify any published studies examining costs in LICs, and only two studies examine lower-middle income countries. Most of the existing studies focus primarily on the direct costs of inpatient care. All studies address costs associated only with acute illness and do not assess costs associated with potential sequelae including wheeze or asthma. While little RSV-specific evidence is available, more robust literature is available for other respiratory infections and other pathogens, which are likely to be informative for RSV. No studies are currently available, however, that directly compare RSV costs with potential proxies that might then be used for economic analyses.

In addition, little RSV-specific evidence is available detailing how households pay for RSV care or whether RSV illness leads to high out-of-pocket payments or catastrophic health expenditures. Despite the scarcity of RSV-specific information, robust literature is available on the effects of out-of-pocket payments for health care and their effects on households.[138–141] Similar effects could reasonably be assumed to be associated with RSV disease, though the scale of RSV-specific household costs is unknown.

The existing literature highlights the insufficient information on the cost of RSV illness in infants, children, and other risk groups and lack of information on cost similarities between RSV and other respiratory illnesses that might serve as a proxy. Specific needs highlighted include direct medical, direct non-medical, and indirect costs for inpatient, outpatient, and non-medically-attended illness from both household and provider perspectives. Information representative of different geographies is especially important for middle-income countries because costs play an increasingly important role in decision-making as incomes rise.

Cost estimates of potential RSV sequelae (e.g., wheeze and asthma) are unavailable in the literature despite their importance, assuming RSV and wheeze or asthma are highly associated. Likewise, no specific evidence is available on how households pay for RSV illnesses, the percentage of cases leading to catastrophic health expenditures, or whether RSV illness costs vary by wealth status or other criteria.

PATH, in collaboration with the Malawi-Liverpool-Wellcome Trust and the University of Liverpool, conducted a RSV cost-of-illness study in Malawi and will undertake similar studies in other LMICs. The Malawi study, those to follow, and subsequent comparison with other illnesses will begin to fill some of the cost-of-illness gaps highlighted above, but research in additional countries will likely be necessary to complement planned work and inform country decision-making.

Cost of delivery

Cost-of-delivery information helps illuminate the costs associated with immunization programs, informs budgeting, and is a critical input to cost-effectiveness studies. While the overall cost of an immunization program is useful, the primary interest is to understand the incremental cost of adding a new vaccine to an existing system. Many cost categories are essential to a costing study (e.g., training of health workers, vaccines, cold chain, monitoring and evaluation, and others). At a summary level, cost-of-delivery studies should typically include both financial and economic costs to inform budgets and the opportunity costs of an intervention.

KEY TAKEAWAYS ON COST OF MATERNAL RSV VACCINE DELIVERY

Progress

- Costs of MI are available from a limited number of country settings.
- WHO guidance and tools developed for influenza MI delivery may be useful for RSV MI.

Work remaining

- Additional details on delivery strategies are needed to determine if existing delivery cost evidence is applicable to maternal RSV vaccine or if additional costing studies are needed.

Existing and missing evidence or conditions on the ground

Several published studies examine the costs of MI programs in LMICs.[142–145] Delivery costs per dose range from $1.35 in Malawi to $1.92 in Brazil for routine delivery. The cost range is substantially wider for

supplementary immunization activities. These studies are a useful guide, but they examine different antigens and delivery strategies and may not perfectly reflect the costs associated with RSV MI and should be interpreted cautiously. WHO developed guidance to inform national decision-makers of the economic considerations related to maternal influenza immunization, including a cost-of-delivery tool.[17] While not developed specifically for RSV MI, applying existing tools may provide an opportunity to increase knowledge of the costs of delivery of maternal RSV vaccines.

Beyond MI, a wealth of information exists on the costs of immunization programs in LMICs and additional efforts are underway to consolidate and generalize this knowledge.[146] Given the variability in delivery costs by program characteristics (e.g., target population, delivery platform, vaccination strategy, etc.), the potential need for additional activities such as disease and safety surveillance, and the variability in the results of existing studies, however, these estimates may not all be appropriate proxies for RSV MI. The potential need to integrate RSV MI into both EPI and ANC programs is a critical difference from existing childhood vaccines and is an area with significant knowledge gaps, though learnings from other vaccine and health programs (e.g., tetanus and human papillomavirus vaccination) can be instructive. These gaps are discussed in section 9.4, Delivery.

The discussion above focuses on the delivery cost of maternal RSV vaccines; however, the lack of public information on the anticipated cost of RSV vaccines for LMIC markets is also a gap. While intervention and delivery cost estimates are important in themselves, they are critical as part of a full budget impact analysis, a component of a larger sustainability analysis, and important for cost-effectiveness studies. Until better data are available, current cost estimates can be used with appropriate sensitivity analysis to inform decision-making.

Demand forecasting, impact, and cost-effectiveness

Demand forecasting informs understanding of the quantity of a commodity needed over time and helps ensure that supply is sufficient to meet this demand. These projections often include a maximum anticipated quantity as well as the pace of scale-up over time. Impact models provide insight into the anticipated effects of an intervention. Common measures of impact include, but are not limited to, the number of cases, clinic visits and hospitalizations, deaths, and disability-adjusted life years (DALYs) averted. Impact studies might also include economic effects, such as the cost of medical care averted. Cost-effectiveness studies strengthen an impact analysis by incorporating the costs associated with the intervention so that outcome measures (e.g., deaths or DALYs averted) can be measured with reference to the cost of achieving that impact. Taken together, these studies can help ensure that intervention demand and supply meet, prioritized interventions achieve substantial impact, and maximum impact can be achieved per dollar spent.

KEY HIGHLIGHTS: RSV DEMAND FORECASTING, IMPACT, AND COST-EFFECTIVENESS

Progress

- PATH completed an initial RSV vaccine demand forecast in 2018, which will be updated as more data become available.
- Results of a RSV impact study for LMICs are expected in 2018.
- Multi-country cost-effectiveness analysis studies are in progress.

Work remaining

- Current modelling should be expanded to include the broader benefits of RSV MI and examine a variety of delivery strategies.
- Additional data are needed to inform country-specific cost-effectiveness studies.

Existing and missing evidence or conditions on the ground

No published demand forecasts for maternal RSV vaccine exist. In early 2018, PATH developed initial demand forecast estimates to inform the 2018 Gavi VIS. These initial estimates provide a useful framework for estimating demand, but are not highly calibrated nor informed by detailed information from countries demonstrating their interest in maternal RSV vaccines. Importantly, RSV is not believed to be well recognized at the country level because it may not be differentiated from other respiratory illnesses. Without such recognition, ensuring country level demand or accurate forecasts will be difficult. Furthermore, existing demand forecast estimates have not yet been used in discussion with industry to ensure appropriate planning so that supply can meet demand from LMICs.

Likewise, no estimates of RSV MI impact and cost-effectiveness across LMICs are publicly available. PATH and the University of Antwerp in collaboration with the London School of Hygiene and Tropical Medicine,

however, developed models of maternal RSV vaccine impact for LMICs. Results of the impact studies are expected to be submitted for publication in 2018, with cost-effectiveness estimates to follow.

Ongoing impact and cost-effectiveness models of RSV MI for LMICs can be improved and expanded by including the broader benefits of RSV interventions and examining strategies to enhance the impact and cost-effectiveness of RSV MI by targeting populations based on risk or seasonal burden of disease. For example, one potential benefit of reducing RSV disease might be to free constrained space, staff, and other resources in pediatric hospital wards and permit additional children to receive high-quality care and indirectly reduce non-RSV mortality. Finally, while many of the issues discussed in this section would enhance global RSV impact and cost-effectiveness models, more country or regionally specific data is also needed for country-specific cost-effectiveness studies to inform country decision-making.

Key questions on the broader benefits of RSV MI:

- To what extent do long-term sequelae influence the health impact and cost-effectiveness of RSV MI?
- How does adding a new intervention to EPI or ANC influence demand for other health interventions or other maternal vaccines (e.g., by incentivizing ANC attendance), affect the health system, or alter the broader health impact of the vaccine?
- To what extent will RSV MI free hospital space for other health conditions?
- To what extent does RSV MI reduce poverty, catastrophic health expenditures, or improve health equity?
- Can RSV MI contribute to reducing antimicrobial resistance by reducing use of antibiotics for suspected ALRI?
- Can RSV MI provide broader benefits such as cognition improvements, improved educational outcomes, or increased productivity?
- Can seasonal vaccination strategies in some geographies and targeted vaccination of at-risk populations enhance vaccine impact and cost-effectiveness?

Financing and budget impact

Budget impact studies are critical to inform understanding of an intervention's financial costs over time. Ideally these studies build on intervention and delivery cost studies as well as estimates of the cost of care that the intervention might avert. Budget estimates then inform the level of financing required for the intervention and potential sources of financing, including internal and external sources.

KEY HIGHLIGHTS: RSV VACCINE FINANCING AND BUDGET

Progress

- Understanding of vaccine financing and sustainability issues is growing, which can help inform RSV MI programs.

Work remaining

- Country-level budget impact studies will be needed to inform RSV MI introduction decisions.

Existing and missing evidence or conditions on the ground

No known country-level budget impact studies of RSV MI programs exist, which is expected since maternal RSV vaccines are not yet available. As a result, required financing needs are uncertain and corresponding funding sources have not been identified. While little RSV-specific information is known, information is broadly available for other vaccines and immunization programs. Published literature demonstrates that financing and sustainability concerns may inhibit support for new vaccine programs.[147,148] Recent analysis also suggests that LMICs provide the largest source of financing for immunization programs (approximately two-thirds), with Gavi making up the bulk of the remaining funding to countries.[148] Maternal health interventions are even more heavily financed by national resources than immunization programs.[149] If current trends are maintained, national resources and Gavi are likely to be the predominant sources of RSV maternal vaccination financing in LMICs.

To summarize, financing needs are not yet known for maternal RSV vaccines, but countries are the largest current source of financing for both vaccine programs and maternal health programming. Gavi plays a

major role in vaccine financing to eligible countries, but no other major sources of external financing are immediately apparent.

Major health economics and financing gaps distilled

Some of the critical health economics and financing evidence relevant to RSV MI exists, though most of this information targets global decision-making rather than country-specific needs. Most of the information needs and gaps are similar to what would be needed for any new vaccine with a few differences due to alternative target populations and delivery strategies. While not necessarily essential to moving RSV MI decision-making and/or introduction, additional gaps can be filled that may be important for demonstrating the additional benefits of RSV MI. Table 4 illustrates the gaps identified as they pertain to health economics and financing.

TABLE 4: Health economics and financing—tiered gaps in evidence or conditions on the ground

Essential and specific to maternal immunization[a]
• No gaps identified in this category.
Essential across immunizations[b]
• 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.
• 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.
• Additional evidence on the costs associated with integrating RSV MI into ANC systems and for vaccination strategies such as campaigns or outreach.
• 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.
• Clarity around Gavi-eligible and non-Gavi eligible countries' ability to afford the vaccines in their current portfolio.
• Lack of recognition of RSV disease burden at the country level.
• Information on manufacturing capacity and ability to meet potential vaccine demand.
Non-essential but supportive[c]
• Information about the costs associated with potential RSV disease sequelae (e.g., wheeze and asthma), which is important assuming evidence of causality. The extent to which this information is useful for LMICs, however, is unknown because the burden may be underappreciated, and treatment may not be common.
• 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.
• Evidence on the broader benefits of RSV MI.
• Evidence on effective strategies to enhance impact and cost-effectiveness of RSV interventions in LMICs.

[a]A gap in information or conditions that is unique to MI and that must be addressed for MI decision-making and/or introduction to move forward
[b]A gap in information or conditions that is generally applicable across vaccines and that must be addressed for MI decision-making and/or introduction to move forward
[c]A gap in information or conditions that, if addressed, could strengthen or accelerate MI decision-making and/or introduction, but is not required to move forward

9.4 DELIVERY

This section examines critical considerations for ensuring optimal maternal RSV vaccine delivery to pregnant women in LMICs. The information presented assumes that a global decision on maternal RSV vaccine introduction has been made based on evidence identified in the preceding sections of this gap analysis and that work on gaps identified as essential above has been completed or is ongoing. In addition, while mAbs are a potentially viable preventive intervention for RSV in LMICs, delivery of mAbs is likely to occur through a very different system and is therefore not addressed in this section, which focuses exclusively on maternal RSV vaccine delivery.

To fully realize the potential of RSV MI, developing clear introduction and delivery strategies is important. This is particularly salient given that immunization services are not currently tailored to provide optimal coverage for pregnant women. While the experience of MNTE programs as well as similar programs that routinely deliver tetanus to pregnant women and non-pregnant women of child bearing age can provide evidence and lessons learned, it also indicates that successful immunization delivery where strong and equitable health systems do not exist will require a systems-wide approach.[18,19] To achieve maximum impact and sustainability, RSV MI needs to be channeled via systems that are best positioned to reach the target population according to individual country contexts.

This section examines needs pertaining to policy; stakeholder awareness, perceptions, and acceptability; and considerations regarding vaccine program implementation. The discussion around these areas takes into consideration the stakeholders involved, including policy/decision-makers, implementers, end-users, and beneficiaries. This section reviews the available evidence, guidance, and needs with an emphasis on domains critical to successful introduction and includes a focus on the two platforms that will require close cooperation and coordination to successfully deliver maternal RSV vaccine to pregnant women—EPI and MNCH programs. It also considers the potential challenges, barriers, and advantages of an integrated platform. The delivery issues covered here are pertinent to the broader health system as well as demand- and supply-side issues that will affect the introduction and uptake of a maternal RSV vaccines. The domains range from operational aspects of vaccine service delivery (including logistics and supply chain) to health system factors that may affect optimal service delivery. Finally, it assesses needs vis-à-vis developing or modifying systems for tracking adverse outcomes in the context of monitoring pregnancy outcomes and AEFI systems as part of a robust PV program.

The feasibility of introducing a maternal RSV vaccine, particularly in LMIC settings, depends on a multitude of factors, many of which are unclear at this early stage of vaccine development. While the following discussion broadly captures general considerations for introduction, available evidence, and outstanding evidence gaps identified by the AMI delivery WG, it recognizes that each country will have additional, unique system and policy needs. Country introduction processes may vary widely based on current systems, the nature of the delivery platform selected, the preferred mechanisms for coordination across stakeholders, and other specific contextual factors. While the opportunities presented here are diverse, they are illustrative, as solutions may be unique to each country. As the essential global challenges are met, countries will have the opportunity to provide inputs and tailor solutions to address context-specific gaps and needs, potentially shortening time to introduction and uptake.

Policy

Introduction of maternal RSV vaccine into LMICs will require global health organizations, immunization and maternal health decision-makers, and ministries of health and finance to work collaboratively to establish global, regional, and national immunization and maternal and child health policies specific to RSV and/or to ALRI in general. These policies will inform system and service delivery recommendations and guidelines, and feed into structures for surveillance and monitoring at the regional and country level. The

KEY HIGHLIGHTS: POLICY

Progress

- In 2015, SAGE encouraged WHO to promote more implementation research to generate generalizable data on the best ways to integrate MI into routine ANC in low-resource settings.
- WHO recommendations for improving pregnancy outcomes through ANC provide an opportunity to strengthen alignment between MI and ANC services.

Work remaining

- Global, regional, and national guidelines, tools, and recommendations will be needed to aid decision-making at all levels.

policy development process will generally follow well-established procedures based on the experience of previous vaccine introductions. Vaccinating pregnant women to protect their infants with a new RSV vaccine requires additional policy considerations and recommendations that necessitate collaboration between immunization and maternal health delivery platforms. In addition, effectively supporting countries with disease surveillance, including potential declines in serious outcomes (e.g., hospitalization), assessment of adverse pregnancy outcomes, and AE monitoring and reporting are crucial to successful maternal RSV vaccine uptake and should be addressed, in part, through policy adoption or modifications.

Existing and missing evidence or conditions on the ground

Global policy

At the global level, WHO's SAGE will consider the range of available evidence pertaining to RSV disease and its vaccine characteristics, efficacy, safety, and health system impacts. A similar advisory group is currently being established within WHO's Department of Maternal Neonatal Child and Adolescent Health (MNCAH) to steer relevant maternal and child health policies and implementation strategies across different health system contexts (the Strategic and Technical Advisory Group of Experts on MNCAH [STAGE]).[150] For vaccines, when SAGE recommends adoption of a vaccine, corresponding WHO and UNICEF decisions and recommendations ensue, as well as financing decisions by Gavi. While this policy process is well established, effective maternal RSV vaccine recommendations will require input and participation from maternal health experts and decision-makers working in collaboration with vaccine experts and decision-makers.

At WHO, several guiding documents and tools will need to be developed or modified to reflect a maternal RSV vaccine recommendation. For example, service delivery considerations will be reviewed via the Immunization Practices Advisory Committee.[151] Tools such as the Effective Vaccine Management Assessment will need to be modified to assess the capacity and effectiveness of country-level vaccine supply chains to manage and deliver maternal RSV vaccine in the context of maternal health systems.[152] Additional recommendations or guidance may also need to be incorporated into global guidelines around the care of pregnant women. WHO recently established updated guidelines and recommendations for improving pregnancy outcomes through ANC.[153] These guidelines provide a framework for helping strengthen overall ANC services and may provide potential approaches for further alignment between MI and ANC services. Global mechanisms and strategies such as the Global Strategy for Women's, Children's, and Adolescents' Health, and the Every Newborn Action Plan, among others, provide supportive policy frameworks that may be leveraged.[154–156]

Regional policy

At the regional level, global immunization policy changes and recommendations are incorporated by Regional Immunization Technical Advisory Groups (RITAGs), which also develop/adapt guidelines and recommendations for routine vaccine delivery, monitoring, and reporting that reflect the needs, cultures, and systems of the respective region. In addition, organizations responsible for setting guidelines and standard procedures for maternal health services (such as WHO, UNICEF, non-governmental organizations (NGOs), and faith-based organizations) will need to coordinate with RITAGs and others to harmonize policies, recommendations, and guidelines for delivering maternal RSV vaccine and other MIs. As yet, regional vaccine and maternal health guidelines and recommendations for maternal RSV vaccine introduction, reporting, and monitoring do not exist.

National and sub-national policy

While the development of global and regional policy decisions tends to follow established processes, each country will develop policies that are consistent with their unique systems, resources, needs, and cultures.[20] National Immunization Technical Advisory Groups (NITAGS), national regulatory authorities, and maternal health technical advisory groups will need to collaborate to reach consensus on national recommendations and guidelines for maternal RSV vaccine introduction, implementation, and training of health care providers.[157] A role also exists for Inter-Agency Coordinating Committees, which in many countries work across ministries, donors, and implementing partners to ensure effective resource utilization and coordination for immunization services. Throughout this process, planning will need to take into consideration that a maternal RSV vaccine is unlikely to be prioritized automatically at the country level given other competing priorities and RSV's lack of recognition on the ground. Substantial work will be needed to share evidence with decision-makers so that they can make informed decisions about RSV MI.

Since maternal RSV vaccine may be the first vaccine licensed specifically for use with pregnant women, precedence is limited for how EPI systems can best accommodate routine delivery within existing maternal

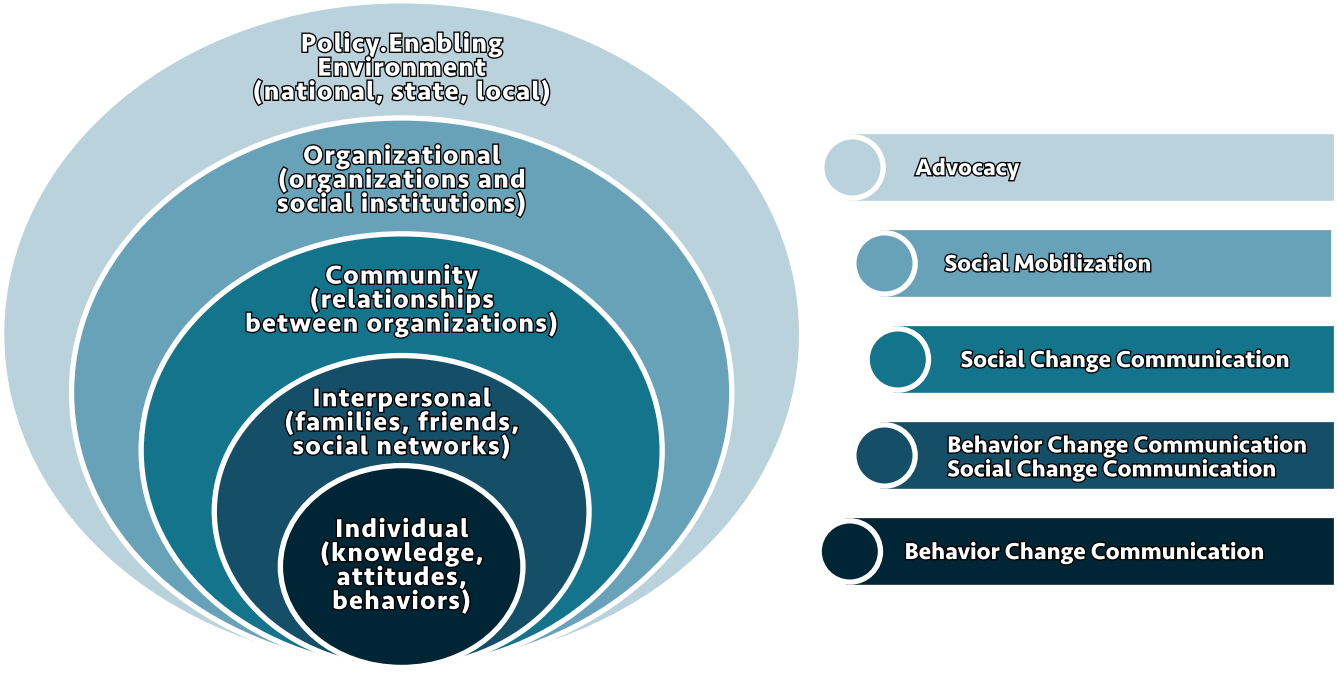
health services and what additional monitoring and surveillance systems will be required. This gap in the knowledge and system design can be partly filled through policy directives, guidelines, and recommendations based on the experience of vaccine demonstration projects in a country or a region. For maternal programs (ANC) to effectively incorporate immunization services, new policy guidance and/or updates to existing policies may be required to streamline coordination and effective service delivery. Supportive guidance and policies promoting integration in the context of health sector reform have existed since the turn of the current century, with the focus primarily on reproductive, maternal, newborn, and child health integration.[158,159] This work should be leveraged for optimizing delivery of RSV MI. In addition, national policies will need to be in place and strengthened to guide AEFI monitoring and reporting systems, which are currently weak in many LMICs.[160] The use of RSV vaccine in pregnant women makes AEFI monitoring and reporting all the more critical. AEFI monitoring and reporting is discussed in further detail later in this Delivery section.

Acceptability, perceptions, and awareness

Evidence and value-based advocacy and communications (A&C) strategies will play a major role in engaging stakeholders, generating maternal RSV vaccine demand, and influencing perceptions and acceptability. Policy development and health intervention adoption at global and national levels is achieved by using stage-appropriate A&C strategies to present relevant, timely, and compelling evidence to decision-makers. As "a strategic effort to achieve change by creating political commitment and an 'enabling' environment," advocacy helps secure the support of decision-makers, policymakers, health practitioners, and others to commit resources and enact policies that bring health solutions to scale.[20,161,162] It can also garner acceptance and support from end users.

Mobilizing demand and influencing acceptability for new vaccines and other health interventions is well established.[20,161,162] Figure 4 outlines how A&C can vary depending on the context and target stakeholder and/or audience according to UNICEF's model of Communications for Development.[163] A&C planning considers the full line of sight from vaccine development through country uptake. In this section, we describe

FIGURE 4. **The varying roles of advocacy and communications depending on context and target audience**



Source: UNICEF's model of communication for development (C4D)

currently available A&C-related information around MI. We also identify the gaps in information or conditions unique to MI that need to be addressed for maternal RSV vaccine decision-making, introduction, and uptake to advance in LMICs.

KEY HIGHLIGHTS: ACCEPTABILITY, PERCEPTIONS, AND AWARENESS

Progress

- Best practices are available and useful for informing A&C strategies around vaccine introductions in general.
- Current MI experiences can inform A&C strategies for RSV MI.

Work remaining

- Evidence- and value-based A&C strategies need to be developed to specifically support RSV MI.

Existing and missing evidence or conditions on the ground

A primary A&C gap identified in this review is that no evidence-based A&C strategies have been designed to inform RSV MI policymaking, acceptability, and demand. The implementation of these strategies will be essential for maternal RSV vaccine decision-making and uptake. Although best practices, lessons learned, and toolkits are available to inform A&C strategies around vaccine introductions in general, A&C information unique to MI and RSV disease is relatively limited. The maternal tetanus, influenza, and pertussis immunization experiences are informative, but few formal studies on the role of A&C are available and most data are from HICs, with some exceptions. Ongoing research through WHO's Maternal Immunization and Antenatal Care Situational Analysis (MIACSA) on vaccine delivery strategies based on lessons from MNT prevention in LMICs includes A&C objectives that promise to be informative when available.[22] RSV as a public health issue has relatively low awareness and priority at the country level (including in the health community) and virtually no RSV-focused A&C-related research is available. (Expert opinion. Expressed at: Allies in Maternal and Newborn Care: Strengthening Services through Maternal Immunization meeting, May 3 and 4, 2018; Amsterdam, Netherlands).

For A&C strategy development to be successful for RSV MI, available resources will need to be examined and critical questions answered to identify the full range of stakeholders/champions across MNCH and immunization sectors; what stakeholders know, think, and care about in relation to RSV and MI; and how to effectively engage and communicate to raise the profile of RSV and MI. The following sections detail the areas where information is incomplete to inform RSV MI A&C strategy development.

Stakeholder awareness, perceptions, and acceptance

RSV MI adoption will require awareness and acceptance by a variety of stakeholders, recipients, and providers, so it is important to understand the drivers that influence each. Raising awareness will be particularly important for maternal RSV vaccine decision-making at the country level, "country level, given the low recognition of RSV as a public health problem in LMICs. WHO PQ and Gavi financing of a maternal RSV vaccine will not automatically generate demand, particularly with already constrained budgets, a crowded vaccine landscape, and the additional system modifications required for its delivery. Understanding how these, and other factors such as moderate vaccine efficacy or limited duration of protection of the vaccine, might influence introduction decisions will be important.

From global to sub-national levels, key opinion leaders (KOLs) are essential for influencing vaccine awareness and acceptance; however, formal KOL identification and engagement planning for RSV MI has not been mapped. At the global level, recognized experts, leaders, or celebrities are common KOLs. At the country level, national policy and other professional leaders are often important, as well as religious leaders, who can strongly influence vaccine uptake in pregnancy.[164]

At the community level, healthcare providers are particularly strong influencers of vaccine acceptance, especially among pregnant women.[165–170] In-depth

Key needs for RSV MI A&C strategy development

- Comprehensive stakeholder identification, including KOLs.
- Understanding of baseline stakeholder knowledge, awareness, perceptions, acceptability, and support needed to raise the profile and achieve appropriate prioritization of RSV and MI, especially at the country level.
- Understanding of how to effectively engage and communicate with key stakeholders and bring them together to generate demand.

discussions between providers and their clients on the risks and benefits of vaccination and to address client concerns have been shown to improve maternal vaccine uptake.[165] In addition to communicating with pregnant women, complementary community engagement with husbands and other family decision-makers is also important.[171-173] Optimal mechanisms to engage communities and communicate information consistently need to be developed to equip key influencers and generate community involvement.[165] Other acceptance barriers include lack of healthcare provider training to communicate complex messages. A well-trained and knowledgeable healthcare worker can explain the risks and benefits of vaccination in a way that can mitigate negative perceptions.[165,174–176] Communications and education will be needed to help healthcare providers discuss RSV MI with their patients and advance vaccine acceptance in their communities.

Maternal vaccine acceptability among pregnant women is also a function of health seeking in pregnancy. The same psychological, financial, social, and physical issues that govern care-seeking in pregnancy may also restrict the accessibility and acceptability of MI.[177] A barrier in access to vaccines administered during pregnancy has been described as a "vaccine-centric focus," in contrast to an "interest-based approach" that incorporates the views of the expectant mother and assumes a mother's strong interest in the welfare of the fetus/infant.[178,179] These same principles are expected to be factors for RSV MI as well.

Understanding baseline awareness and perceptions of MI and RSV disease among policymakers and other key stakeholders at the global, national, and subnational levels is fundamental to developing effective A&C strategies. Currently, however, information is insufficient to understand the full scope of awareness gaps and perception barriers. This gap extends from global and regional policy-makers to NITAGs and reproductive and MNCH working groups in LMICs. It also extends to the community level where awareness and perceptions, especially among healthcare workers and pregnant women, can affect vaccine uptake. Most research evaluating MI awareness and perceptions among these groups originates in HICs around influenza and pertussis MI.[165] Evidence from LMICs, namely Malawi and El Salvador, identifies general support among mothers, healthcare workers, EPI managers, and policymakers for MI, but suggests that high coverage would require

TABLE 5: **Summary of stakeholder categories across immunization and maternal child health disciplines with prospective roles in maternal RSV vaccine introduction**

Global	Regional	National	Sub-national
• International organizations / normative bodies • International non-governmental organizations (NGOs) • Global health funders • Scientific community • Government donors • Manufacturers • International professional associations	• Technical advisory groups (TAGs) • International organization regional offices • Scientific community • Faith-based organizations	• National immunization TAGs • Reproductive MNCH working groups • Inter-agency coordinating committees • Government ministries • International organization country offices • Professional organizations • NGOs • National PV centers	• Pregnant women/health care decision-makers • Healthcare providers • Religious and/or community leaders • NGOs and other community groups • Expanded Programme on Immunization (EPI) managers • Media (traditional and social) • Vaccine champions and opponents

Sources

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2. InScale. *InSCALE Stakeholder Analysis Report*. (2010).
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4. McKinsey & Company. Mapping Influencers in the Vaccine Introduction Decision-Making Process in Developing Countries. (2007).
5. Smith SL, Shiffman J. *Soc Sci Med*. (2016).

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training, advocacy, and communication.[172,173] Overall, lack of awareness and education among healthcare providers around MI, specifically on vaccine safety and potential benefits to the newborn can inhibit their ability to communicate information about maternal vaccines to their patients. In Thailand, for example, lack of national policy knowledge and policy ambiguities were found to be major barriers for healthcare providers recommending influenza vaccination to pregnant women (even if favoring the intervention).[180] Furthermore, lack of knowledge and awareness of RSV, especially at the country level and among healthcare workers, is another barrier that, if not addressed, could prevent RSV from being prioritized appropriately. Currently, RSV is a low or non-existent priority in many countries. A&C strategy development will need to determine how to share technical information appropriately and effectively across a range of stakeholders, including communities, health care workers, and decision-makers.

Stakeholder identification and engagement across sectors

An early step in A&C strategic planning is identifying the full range of stakeholders (including allies, undecided potential allies, and opponents) and how they can collaborate. For RSV MI, this includes stakeholders from global to sub-national levels and across immunization and MNCH sectors. Ongoing work through the Gates Foundation and Rabin Martin to identify priorities and concerns around MI within the MNCH community is providing useful information, including stakeholder convening's in 2015 (Berlin, Germany) and 2018 (Amsterdam, Netherlands).[149] Furthermore, some studies in LMICs have helped to categorize MI stakeholders, which provides a foundation for supporting an A&C strategy specific to RSV MI (see Table 5). However, a plan to identify the full range of specific stakeholders and how to engage and sensitize has not yet been formally developed.

Messaging and modes of communication

Current literature identifies evidence- and value-based messages that resonate with stakeholders as key to an effective A&C strategy.[181,182] An essential gap is that messaging strategies for acceptability and raising the profile of RSV disease and maternal RSV vaccine at various levels, especially at the country level, have not been formally assessed. Determining the messages and terminologies that resonate with audiences, promote common understanding, and garner support/collaboration (especially across MNCH and immunization stakeholders) will be critical for a maternal RSV vaccine as it creates precedent and may impact current and future maternal vaccine acceptance and prioritization of RSV. Within this larger gap is a lack of research on the fundamental term "maternal immunization" to more formally understand the perceptions that it carries and preferred alternatives, if appropriate. Similarly, research is lacking on how to position RSV disease, especially around how to describe and discuss RSV disease appropriately across different stakeholders. Modes of communication also matter and differ between populations, underscoring a need to understand how various stakeholders prefer to receive information.[183]

Programmatic considerations

This section examines key programmatic considerations for maternal RSV vaccine introduction and uptake. While special vaccination campaigns and outreach services are briefly discussed, the focus is on delivery via routine service delivery channels. The effective involvement of MNCH and EPI in maternal RSV vaccine delivery presents issues and challenges that each system will need to address to ensure effective introduction of this vaccine. The prospect of integrating maternal RSV vaccine delivery into the ANC platform will provide an opportunity to leverage lessons from other efforts that have integrated vertical programs into maternal health.

The only vaccine currently recommended for pregnant women as part of WHO's recommendations for ANC is TT, however, global- and country-specific recommendations (and introduction experiences) also exist for other vaccines (e.g., for seasonal influenza and pertussis) administered to pregnant women.[153,184] Existing global guidance documents for introducing seasonal influenza vaccine in pregnant women, for example, can provide a blueprint to inform delivery strategies for maternal RSV vaccine.[185,186]

KEY HIGHLIGHTS: PROGRAMMATIC CONSIDERATIONS FOR RSV MI DELIVERY

Progress

- EPI platforms are mostly well-established and functional in LMICs.
- TT vaccination in pregnant women provides insight into maternal vaccine delivery.
- Globally, about 82% of pregnant women receive at least one ANC visit.
- More opportunities to vaccinate pregnant women through ANC given additional contacts recommended by WHO.

Work remaining

- EPI will need to expand or modify service delivery, logistics, and health system management plans to incorporate maternal RSV vaccines.
- Close coordination between EPI and ANC will be needed for most maternal RSV vaccine introduction and delivery scenarios.
- Methods to optimize vaccine coverage via routine service delivery channels need to be identified.
- Causes of high levels of drop-off between ANC 1 and ANC 4+ visits need to be addressed.

Existing and missing evidence or conditions on the ground

Routine maternal RSV vaccine delivery will require collaborative involvement of EPI and MNCH programs. Unique factors for both EPI and ANC platforms are explored herein, followed by a discussion of the specific systems and information needs pertaining to these platforms working together to deliver the vaccine in a 'typical' LMIC context.

EPI considerations for vaccine delivery

Established over 40 years ago, the EPI is the standardized system for immunization program delivery and management, including enabling vaccine supply and logistics systems to receive, inventory, store, and transport vaccines at the proper temperature and deliver them to target populations in in a timely manner. It also provides mechanisms for monitoring and reporting vaccine coverage, stock outs, and delays.[187] In most countries, EPI commodity delivery begins from a central point and cascades to provincial, district, and sub-district levels, as well as to health facilities, outposts, or campaign outreach sites for administration. EPI is generally seen as an effective system for vaccination delivery and service monitoring. Although primarily designed for and largely focused on delivering childhood immunizations, EPI also includes TT-containing vaccines for pregnant and non-pregnant women of reproductive age.[193] Many LMICs face challenges to vaccine delivery and uptake due to a range of factors, including increasing numbers of vaccines in the system (which can overburden a constrained cold chain and transport system); lack of trained healthcare workers; inaccurate and/or incomplete reporting (notably with insufficient monitoring or support for analysis and use of data at input levels); and geographic isolation of many regions in LMICs.[187]

Successful maternal RSV vaccine delivery will require the standard information related to the vaccine characteristics that is required of all new or modified vaccines entering the EPI system (e.g., formulation, presentation, cold chain requirements, packaging, schedule, and administration). Since no maternal RSV vaccine is yet approved, the information around logistics is not yet developed, but will inform delivery

Standard EPI elements that need to be expanded or modified to accommodate RSV MI

Service Delivery

- Coverage
- Surveillance
- Communication/social mobilization

Logistics

- Cold chain
- Vaccine management
- Transport

Health system management

- Planning
- Financing
- Human resources

Source: Pathirana J, Nkambule J, Black S. Vaccine (2015).

strategy. Given the standard nature of these information needs, they do not constitute gaps in knowledge but are yet-to-be-completed steps in maternal RSV vaccine and program delivery development. In addition to the vaccine characteristics, the EPI system, in concert with ANC, will need to expand its management protocols to include maternal RSV vaccine delivery-related forecasting, monitoring, data collection, logistics, and reporting. The introduction of a new vaccine provides an opportunity to improve current immunization programs and strengthen best practices; however, the activities themselves may pose logistic and human resource challenges to existing operations.[188]

Reaching pregnant women through ANC

ANC service utilization has improved markedly over the last two decades, which has greatly increased access for underserved populations.[189] Globally, around 82% of pregnant women access ANC care at least once during pregnancy.[190,191] Only three in five (62%) pregnant women, however, attend at least four ANC visits. In Sub-Saharan Africa alone, about four women in five (80%) attend at least one ANC visit, though only about half of the women (52%) receive four or more visits, as previously recommended by WHO through the focused ANC care model.[191,192] Opportunities to vaccinate pregnant women via this channel, however, may increase in the coming years given new global guidance and improved care seeking and access—even in the most resource constrained environments.[190] This section examines the available evidence around aspects likely to affect maternal RSV vaccine delivery via ANC services and identifies the gaps in the evidence needed for decision-making around maternal RSV vaccine launch and uptake at the country level.

ANC is a platform for delivering a wide range of health services (e.g., screening, behavior change communication [BCC], and disease prevention and management), including vaccination of pregnant women. The most recent WHO ANC recommendations increase contacts between pregnant woman and ANC services from four to eight.[153] Four of these proposed contacts (at 26, 30, 34, and 36 weeks into pregnancy) occur during the proposed window for delivering maternal RSV vaccine. The recommendation around ANC visit timing could increase the opportunities to provide maternal RSV vaccine to pregnant women. The care that women receive in ANC varies widely, however, between and within countries based on the number of visits, the category of provider (doctor, nurse, midwife, other), and the quality of care provided.[194] Identifying mechanisms that support consistently achieving the recommended number of contacts with quality care remains a significant gap and hinders the likelihood of achieving desired coverage for RSV MI. A review of evidence found no consistent relationship between ANC coverage and the proportion of women receiving two or more doses of TT-containing vaccines (TT2+) (see Table 6). If access to vaccines is low, the EPI usually compensates for poor coverage

TABLE 6: **Mean number of ANC visits per pregnancy and TT2+ coverage rates in countries by income category**

World Bank Income Category	ANC visits in Pregnancy (%)				TT2+ Coverage (%)
	No antenatal visits	1 ANC visit	2 to 3 ANC visits	4 or more visits	
Low Income (27 countries)	11.4	4.0	32.0	50.8	83.7
Lower Middle Income (34 countries)	10.9	4.2	19.2	63.5	86.5
Upper Middle Income (16 countries)	6.3	2.4	11.2	75.1	89.5
All (77 countries)	10.2	3.8	22.3	62.3	86.8

Data sources:

1. The DHS Program STATcompiler website. https://www.statcompiler.com (accessed December 22 2017).
2. WHO Immunization, Vaccines and Biologicals. Data, statistics and graphics web page. http://www.who.int/immunization/monitoring_surveillance/data/en/ (accessed December 21, 2017).
3. World Bank Data Help Desk. https://datahelpdesk.worldbank.org/ (accessed December 21, 2017).

by providing outreach services and supplemental immunization activities such as national or sub-national vaccination campaigns. This approach may not be most appropriate for maternal RSV vaccine delivered programmatically through ANC. In addition, it will be very costly and likely unsustainable from a financial perspective, compared to supporting vaccine delivery via routine services.

With regards to continuity of care in LMICs, few follow-up mechanisms exist to ensure continuity for pregnant women, particularly after the initial consultation and for women who do not seek any ANC. ANC outreach by community health workers (e.g., by Lady Health Workers, Family Health Assistants, etc.), however, often provides access to these populations, including for vaccination. The use of mobile devices and applications for public health purposes (mHealth technologies) provide further opportunities to provide BCC messages and improve follow up. Studies in Tanzania, Kenya, and Ethiopia demonstrate that mobile phone text message reminders improve the likelihood of pregnant women attending ANC visits. Results around improving vaccine coverage with mHealth interventions, however, are mixed.[195–197]

Vaccine delivery and ANC integration

While each country will develop custom delivery strategies for RSV MI based on their needs and circumstances, most country EPI and MNCH programs will likely require collaboration to ensure streamlined vaccine delivery to the target population. This section discusses an integrated delivery model in which EPI and MNCH programs work together to provide maternal RSV vaccine through ANC services. Assumptions include that midwives or other ANC health care providers vaccinate pregnant women in the same location where ANC is provided and coordinate with the EPI for the management of vaccine logistics, supply, and cold chain. This section examines the advantages, challenges, and opportunities that come with such an integrated model. The outstanding information needs that must be met to streamline introduction and sustain uptake of a maternal RSV vaccine are also presented.

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Integration has the potential to strengthen collaborations between traditionally siloed EPI and MNCH programs, not only for delivering a maternal RSV vaccine but in other ways as well. It would capitalize on EPI's robust standard operating procedures for ensuring safe, secure, and effective vaccine storage, handling, transport, and stock management. An integrated cold chain that allows for incorporating pediatric and maternal medicines with vaccines to leverage the existing EPI cold chain would also address the often relatively fragile cold chain for pharmaceuticals. This integration, while permissible, has been hitherto limited.[198] At the same time, evidence demonstrates that an integrated delivery model would maximize reach and health impact via the use of a platform (ANC) that provides a more holistic approach to disease control management of care and health promotion.[199,200] Additionally, it would engage ANC providers, who are critical to improving vaccine coverage and uptake in pregnant women.[175] Finally, women's preference for integrated, quality services warrants designing MI delivery services around women rather than around the facility or other vertical programs.[201]

Integration also has the potential to strengthen the broader health system and bring ancillary health benefits, particularly around uptake and perceived quality of services. If adequately supported and maintained, an integrated system carries a higher probability of impact (including coverage of immunization services, ANC uptake, continuity of care, and improvements in health outcomes) and sustainability over the long term. Experiences from integrating previously siloed programs such as malaria control (e.g., intermittent preventive treatment in pregnancy) and HIV mother-to-child-transmission prevention into ANC illuminates the possibility for greater sustainability and program efficiency.[202–205] Experiences from these realms, however, also highlight the need to ensure adequate work load and skill capacity for ANC maternal RSV vaccination providers. Information is also needed regarding the effect of vaccine introduction on the quality of ANC service delivery and the potential effects on other specific ANC services.[206] Logistic issues and disruptions of service delivery have been identified as significant

challenges to integration, particularly for more complex interventions.[207] As with any public health intervention, successful introduction and scale-up will need to account for factors such as current national and local policies defining the types of medical procedures that can be delivered by various providers. This is particularly relevant for delivering injectable vaccines through outreach care services. For example, lower-level health care providers, including certain community health workers, may be prohibited from administering injectables.

Case studies on community and health worker perceptions and preferences around integrating health services with routine vaccinations reveal that communities generally support integration.[208] These studies also show that integrated services may have the potential to increase service utilization and possibly reduce the stigma of certain services. Evidence from Honduras, for example, provides an example of successful vaccine delivery integration with preventive and health-promotion services, and could serve as a template for other similar LMIC settings. [208-210] Keys to success included planning and coordination and ensuring computability of service delivery.

Successful EPI and ANC coordination will require the collaboration of technical experts and thought leaders from both disciplines, who will need to identify the mechanisms for harmonization, establish effective management and reporting structures, and ensure sustainable financing mechanisms. Landscape analyses will be needed to provide information on the range of current platforms used for delivering maternal vaccines and the service providers involved in providing vaccination to pregnant women (MNCH or EPI staff). This analysis will also be needed to identify optimal delivery models across different country settings and factors that impact integration and vaccine uptake. Additional information needs pertain to accountability, key responsibilities, and reporting lines specific to vaccine logistics and immunization program quality (e.g., cold chain, waste management, inventory management, and other considerations).

WHO's MIACSA project is conducting an in-depth assessment of maternal vaccine delivery strategies and systems in LMICs.[22] One project objective is to evaluate the collaboration or delineation of the EPI and ANC delivery systems in LMICs and provide suggestions for improving and strengthening maternal vaccine delivery services. The results of this analysis, expected in March 2019, should fill some of the gaps in knowledge and understanding about the mechanisms for EPI and ANC alignment, and recommend areas for strengthening. Outstanding questions around optimal platforms for maternal RSV vaccine introduction, however, will require *de novo* evidence from countries that can address this question for different geographies and stages of social and economic development.

Another key issue that has not been addressed for MI is sustainable funding. Beyond the vaccine, the funding mechanism for an integrated platform has not been identified, and costs associated with integration, such as training, facility and cold chain enhancement, and outreach support, will be above and beyond costs associated with current routine EPI services. Additional unknowns are whether such a platform could contribute to a wider health system-strengthening effort in ANC and, if so, how it would be resourced.

Other information and evidence gaps are less critical to introduction but would aid policy and uptake strategies. This includes determining the potential impact of maternal vaccines on maternal health care uptake along the continuum of care. Evidence is also needed around opportunities for achieving vaccine delivery efficiencies through integration with other health services, especially for populations not receiving healthcare through formal channels. Finally, implementation science efforts to identify efficiencies, particularly in the context of monitoring the new ANC guidelines, will also be needed.

Monitoring and safety surveillance

Currently, systems for monitoring health outcomes in pregnant women and newborns in LMICs are limited.[211] Existing systems may lack the sensitivity and accuracy needed to track severe maternal morbidity and adverse birth outcomes including fetal death, prematurity, and congenital malformations.[160] Vertical programs advocate different indicators, which has resulted in the absence of a standard list of indicators for health management information system tracking. Successful routine vaccine delivery to pregnant women, regardless of delivery mechanism, will require a robust tracking system for adverse pregnancy outcomes and AEFI monitoring and surveillance.

While the experience with TT-containing vaccine provides some AEFI system guidance, TT vaccination is well established in LMICs and its safety monitoring relies primarily on passive surveillance. Maternal RSV vaccine will be new and intended specifically for delivery in pregnant women, necessitating an active surveillance system to collect information on safety issues in a timely fashion so that action can be taken to remediate any concern, sustain public confidence, and ensure the smooth operation of the immunization program.

In many LMICs, monitoring and safety surveillance systems are currently inadequate.[160] Where they do exist, RSV MI is likely to add additional strain to an already burdened system. Questions and gaps exist about how the tracking and record keeping of pregnant women currently occurs and the capacity of EPI systems and MNCH services to meet existing monitoring and surveillance requirements and standards. Additional gaps specific to MI include how to better collect needed data (e.g., pregnancy registration, birth outcomes, and fetal anomalies); update training and reporting requirements, establish quality standards, and improve system management.

KEY HIGHLIGHTS: RSV MI MONITORING AND SAFETY SURVEILLANCE

Progress

- Many countries and global organizations are introducing and/or improving data collection and surveillance systems.
- Civil Registration and Vital Systems use is expanding.

Work remaining

- Systems for following and assessing outcomes in pregnant women requiring longitudinal integrated health records need to be strengthened and/or created.
- More comprehensive use of birth and death reporting systems such as the Health and Demographic Surveillance Systems is needed in LMICs.
- PV and AEFI monitoring and reporting are not well established or adequately functioning in most LMICs.

Existing and missing evidence or conditions on the ground

This section examines existing mechanisms for monitoring pregnancy outcomes, the gaps and weaknesses in current systems, and needs as they relate to introducing a new maternal vaccine. A discussion follows of monitoring and surveillance for AEFIs.

Monitoring pregnancy outcomes

Coordinated methods of monitoring health outcomes in pregnant women and newborns (including systematic tracking) are needed to provide a baseline for AEs and risk attribution. Data collection and surveillance on pregnancy and newborn outcomes are generally weak in LMICs.[212] Civil Registration and Vital Systems (CRVS), the primary source of vital statistics in many LMICs, may be poorly functioning or non-existent. Further, individual medical records currently kept are insufficient to track pregnant women and their babies over time or to link mother with baby. Also, births and deaths in LMICs often take place outside the formal health system, increasing the probability that these vital events may not be reported. Documentation in medical records is poor and copies may not be properly stored. Given its importance to overall health systems, substantial efforts are being made to strengthen CRVS in LMICs. In the last decade, many countries have begun to improve their CRVS, often in consonance with broader efforts to streamline administrative systems (e.g., e-governance).[213] Information technology use has strengthened CRVS and accelerated efficient data collection and management. A review of global evidence indicates that despite ongoing challenges, CRVS systems in countries are improving recordkeeping, including deaths and cause-of-death information.[194]

Other surveillance systems in place for mortality and morbidity outcomes in pregnancy and the neonatal period include the maternal and perinatal death surveillance and response (MPDSR), which includes identification and notification, audit, and review for cause-of-death for maternal and perinatal deaths.[214,215] In some settings, integrated disease surveillance and response for notifiable diseases is used to report vaccine-preventable diseases as well as maternal and neonatal deaths. Other systems include the Health and Demographic Surveillance systems (HDSS), which monitor births, deaths, migration, and key health indicators of a population within a defined geographic area with households mapped and numbered. Limitations to the HDSS include underreporting based on frequency of visits, recall bias, informant literacy, and difficulty in accurately recording gestational age and cause of death. Cultural beliefs about reporting pregnancy loss and early neonatal deaths also may contribute to event underreporting.

Pregnancy (exposure) registries are often used to monitor the safety of pharmaceuticals and medical devices used during pregnancy by prospectively enrolling women at their first ANC visit and assessing outcomes of women and their children. An advantage of pregnancy registries is their prospective design, which reduces the risk for recall bias. It also makes linking the mother with her offspring possible. Most registries currently exist only in study settings and few pregnancy registries exist in LMICs.[216] Registry data limitations may include

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reporting bias toward high risk pregnancies, women attending ANC, late disclosure of pregnancy, and late ANC enrolment. Home births and migration may also result in loss to follow up since most of these registries are facility based. To effectively support RSV MI, pregnancy registries and records will need to be part of the routine health information system.

Further needs include standardized case definitions of key events in pregnant women and newborns and improved e-health reporting technologies. Decisions on investments on systems strengthening to address these monitoring needs for both pregnancy outcomes and vaccine systems vis-à-vis maternal RSV vaccine introduction should be preceded by formative research on required scope, scale and relevant geographies (early adopter or all introducing countries) to determine the optimal return on investment

Some ongoing efforts provide opportunities to synergize monitoring and surveillance needs for RSV MI. WHO's Department of Reproductive Health Research is working on developing electronic registries and the department of MNCAH is undertaking the Mother and Newborn Information Tracking of Results (MoNITOR) project with the aim of harmonizing maternal and newborn indicators. They are also developing norms and standards.[217] Several larger birth defect surveillance initiatives could also provide useful data such as the Newborn and Birth Defects Database in SE 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.[218–222]

Monitoring vaccine safety [a]

Surveillance systems are key to monitoring vaccine safety and addressing safety concerns in a timely manner.[223] Passive surveillance systems typically have low reporting rates, limiting their ability to detect rare events. Furthermore, active surveillance capacity in LMICs is not currently sufficient. Most SAEs are rare and surveillance systems must cover a large cohort of the population to detect rare events or a pre-specified increase in rates of AEFI. Understanding background AE rates is especially critical for MI because AEs occur in pregnancies that are unrelated to vaccination. Robust data collection is, therefore, needed to accurately detect AEFI. Maternal vaccines may result in AEs in the mother or in the infant before or following birth and require extended follow up and additional data collection to assess safety. Current gaps include data on maternal and neonatal AE background rates; coverage and quality of vaccine PV systems, including information technology capacity; insufficient personnel training (particularly of MNCH staff, who may have limited training and exposure in AEFI reporting); the lack of data sharing and communication models; and the inability to accurately track vaccine administration and coordinate data flow. Coordinating efforts to strengthen vaccine PV are strongly needed.[160]

Opportunities on these fronts exist and progress is being made. As delivery systems develop for maternal RSV vaccines, linkages with other systems such as local health information systems, population level surveys, the WHO Global RSV Surveillance Pilot, MPDSR, and facility-based registries such as the Latin American Center for Perinatology's Perinatal Information System can be leveraged to monitor AEFI and MI safety.[6,224–226]

a. While the Product results section focuses on high level safety gaps specifically related to maternal RSV vaccines, this section deals with broader surveillance issues including systems in place for pharmacovigilance.

Given the unique MI surveillance needs, any system used to monitor maternal RSV vaccine safety will need to be tailored to fit these needs and the local context. The Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) has developed a comprehensive set of references and analyses of MI safety monitoring in LMICs, including a roadmap for improving AEFI reporting systems.[160] It explores the strengths and weaknesses of current systems as well as approaches to system strengthening and should form the basis for addressing gaps in the current systems.

Ethical considerations

The traditional approach to ethical considerations for MI relies on the conclusion that a vaccine should only be given if its disease risk is serious for both mother and child.[178] In light of this and given the negligible known health impact of RSV on pregnant women, maternal RSV vaccine introduction may entail new ethical implications. A recent movement has emerged around reorienting the ethical framework for MI to focus on the mother's right to protect her child using an interest-based approach,[179] after which:

- Incorporates the interests of expectant mothers at its core;
- Assumes that a mother's interest in the welfare of her fetus/infant is at least as concrete and universally understood a consideration as an appeal to protecting her autonomy;
- Includes women in developing ethical guidelines and;
- Empowers the mother to consider her interests, including a pregnant woman's choice around receiving maternal vaccines.

Excluding sub-populations of pregnant women from vaccine research (e.g., adolescents and HIV-infected women that can often represent a considerable proportion of the pregnant women in some settings), has inherent risks in terms of vaccine recommendation and label development. Clinical plans for vaccines targeting pregnant women should include pregnant women and these important sub-populations. No broadly accepted ethical framework exists for clinical research in pregnant women. For example, minimal risk is not well defined, which has led to important knowledge gaps in vaccine response for both early and late pregnancy and appropriate safety evaluation. Only recently has there been an update to the labeling of vaccines, which allows for more specific information on vaccine labels to assist healthcare providers.[227] Similarly, collaboration between human rights advocates, ethicists, and health researchers will be important to identify appropriate ethical frameworks for MI, which may differ by context especially with respect to pregnant populations with additional considerations (e.g., co-morbidities).[228] Ongoing work around the ethical issues of MI in the context of outbreaks may also guide thinking around ethical frameworks in these populations.[229]

Acceptability of vaccines intended for pregnant women will be important for vaccine investment, demand strategies, and effective implementation. Ongoing work in Kenya and Latin America by researchers from Emory University (to be completed summer 2018), and studies in Senegal and The Gambia led by Medical Research Council (MRC) Unit seek to understand pregnant women's motivations and challenges with accessing vaccination services and would address some of these questions.

KEY HIGHLIGHTS: ETHICAL CONSIDERATIONS

Progress

- A growing movement is reorienting the ethical framework for MI to focus on a woman's right to protect her child.

Work remaining

- Studies are needed to understand the impact of RSV MI on pregnancy in sub-populations such as adolescents and HIV-infected women.
- Ethical frameworks for MI need to be developed.

Major delivery gaps distilled

The gaps in information delineated below generally pertain to the information and system needs that are required for maternal RSV vaccine rapid launch and uptake at the country level, with some global considerations where applicable. Gaps in knowledge and understanding specific to maternal RSV vaccine are listed in Table 7 below. The first category lists essential gaps in evidence and conditions unique to MI introduction and delivery, the second category pertains to gaps relevant to any new vaccine being introduced. The final category pertains to information that would be supportive, but not essential in informing country decision-making around RSV MI.

TABLE 7: Delivery—tiered gaps in evidence or conditions on the ground

Essential and specific to maternal immunization[a]

- Information and data across settings on current mechanisms and modalities for ANC delivery and their capacity to routinely deliver vaccines.
- Information on appropriate management models and effective coordination mechanisms between EPI and MNCH programs to drive decision-making, strategy development, and effective implementation of RSV MI.
- The costs associated with providing MI through ANC, including those associated with strengthening the ANC infrastructure.
- Identifying funding mechanisms for supporting RSV MI integration between EPI and ANC.
- Defining cold chain, logistical, and vaccine management requirements and processes for maternal RSV vaccines.
- Understanding the drivers and barriers for RSV MI acceptance and uptake in LMIC contexts.
- Evidence-based A&C 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.
- Strengthened immunization monitoring and surveillance systems in LMICs to reliably track and report pregnancy and birth outcomes, vaccine coverage, and AEFIs.
- Background rates of pregnancy complications and adverse pregnancy outcomes in LMICs to provide evidence of maternal RSV vaccine safety and to support vaccine acceptance with regards to outcomes that may be temporally associated, but not related to, vaccination.
- Information on RSV disease and MI to support stakeholder awareness, engagement, and advocacy at regional and country levels.
- Data on the impact of integrating RSV MI with existing ANC services on ANC quality and coverage.

Essential across immunizations[b]

- The WHO Effective Vaccine Management assessment tool does not include maternal RSV vaccine delivery and management assessment variables.
- A technical field manual on maternal RSV vaccine introduction for LMICs.

Non-essential but supportive[c]

- Data on the seasonal distribution of RSV in LMICs to inform optimal vaccine delivery strategies.
- Data on RSV disease burden in specific sub-populations to inform appropriate vaccination strategies for high-risk populations.
- 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.
- Information on effective mechanisms for following up with women that miss visits or do not seek ANC in LMICs.
- 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.
- Strategies to improve vaccination coverage in women who do and do not receive ANC via the formal healthcare system, including missed vaccination opportunities.
- Additional evidence on appropriate framing and messaging of RSV MI for different stakeholder groups.
- Information on maternal RSV vaccine effectiveness, safety, and cost-effectiveness in LMICs to inform global and country decision-making.
- Despite international standards, national regulatory authorities in LMICs generally lack the legal authority to enforce AE reporting requirements.
- Incorporating women's perspectives into vaccine development and introduction planning—both as policy makers and end-beneficiaries.

[a]A gap in information or conditions that is unique to MI and that must be addressed for MI decision-making and/or introduction to move forward
[b]A gap in information or conditions that is generally applicable across vaccines and that must be addressed for MI decision-making and/or introduction to move forward
[c]A gap in information or conditions that, if addressed, could strengthen or accelerate MI decision-making and/or introduction, but is not required to move forward

4/ CONCLUSION

Maternal RSV vaccines have the potential to improve infant health and survival in LMICs. The nature of these vaccines and their delivery to pregnant women provides opportunities and challenges beyond those associated with traditional infant immunization. This report describes the evidence and conditions needed by global and country decision-makers, public health program planners, and implementers to introduce and optimize RSV MI in LMICs. It summarizes evidence across RSV disease, vaccine product, health economics and financing, and vaccine delivery, and highlights critical gaps that, if left unfilled, could delay or preclude vaccine introduction and use in countries that need it the most.

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While the full collection of gaps described in this report represent the breadth of information required, they can be distilled into three overarching themes.

Awareness and perceptions

Awareness and perceptions of RSV and maternal vaccines will drive decision-making around vaccine introduction as well as acceptability and uptake of maternal RSV vaccines. While pervasive, RSV disease remains largely unrecognized, particularly at the country level. Decision-makers will require nuanced RSV disease burden data from LMICs to understand the potential impact of a maternal RSV vaccine when prioritizing interventions. A strong value proposition for maternal RSV vaccine will also be needed, and decision-makers will need to consider its cost-effectiveness, budget impact, and affordability.

Concerted effort will be required to improve knowledge and awareness of RSV disease and protection strategies, including MI, among healthcare workers, pregnant women, and their key influencers. In order to generate demand, strategies for communicating information need to be appropriately tailored to local contexts and account for community and provider perceptions.

Improved monitoring of pregnancy outcomes and safety surveillance

Strengthening or instituting systems *de novo* to monitor health outcomes in pregnant women and newborns before vaccine introduction is needed to provide critical baseline data for risk attribution and inform strategies around risk communication and vaccine hesitancy. Once the vaccine is introduced, robust pharmacovigilance and adverse events monitoring and reporting will be needed.

Localized delivery strategies

The global introduction of a novel maternal RSV vaccine will require countries to tailor strategies and mechanisms for vaccine delivery to their individual contexts. Given the target population, this will most likely require coordination between EPI and MNCH stakeholders and may necessitate modifications to current service delivery, logistics, and management systems. While there are lessons to be learned from other experiences, information will be required to identify optimal delivery models across contexts and inform harmonization across capacity building, management, and reporting structures. Identifying sustainable financing mechanisms will also be critical.

The considerable evidence that exists or is currently being generated underscores the headway already made towards advancing RSV MI and is cause for optimism about forward progress. Ongoing efforts, including the current Ph3 vaccine safety and efficacy trial of

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the Novavax maternal RSV vaccine candidate, health economic analyses, and work conducted by projects such as WHO's MIACSA and others are generating evidence that will fill a number of the essential gaps identified in this report. Of the 57 identified gaps, 17 are classified as essential and unique to RSV MI and an additional 12 are essential across immunizations more generally. A number of efforts are currently generating data that will fill or contribute data to many of the 30 essential gaps by the time a maternal RSV vaccine receives WHO recommendation. Nonetheless, new efforts will be needed to address other key gaps identified in this report. As the RSV landscape continues to evolve, the work already in progress and additional data called for here will support efforts to navigate the pathways and solutions for preventing RSV disease to help infants survive and thrive, no matter where they live.

STRENGTHS AND LIMITATIONS OF SCOPE AND APPROACH

A strength of this gap analysis is that it is being conducted several years in advance of vaccine availability, providing time to identify relevant gaps and engage stakeholders that will be key to successful vaccine uptake in LMICs. Building upon this strength is the scope of our analysis, both in terms of stakeholder contributions and content. Over sixty global experts, representing a variety of disciplines and diverse perspectives, contributed to this report. The topics included are comprehensive, spanning RSV disease burden, vaccine development, health economics and financing, and vaccine delivery specific to

LMIC contexts. Finally, the Secretariat provided multiple opportunities for members to iteratively review AMI work products.

Despite these strengths, our approach has several limitations. One is that, although AMI membership is expansive, it does not include all relevant stakeholders. Also, while AMI made a concerted effort to include perspectives from LMICs, members were not necessarily representative of the vast differences in countries with respect to a number of important factors including disease burden, surveillance capabilities, vaccine and ANC infrastructure and practices, and factors associated with vaccine demand. Another limitation is that systematic reviews of the literature were not conducted for all topics covered by this report. We relied on subject matter experts and AMI member recommendations for some topics, which may lead to some relevant information being omitted. Also, it is possible that there is additional ongoing work that could contribute to filling some gaps that is currently unknown to AMI members. This work incorporates iterative input from 62 AMI members and such a collaborative approach is effort- and time-intensive. While the series of iterative reviews encouraged a focus of results on those acknowledged as relevant across disciplines, the Secretariat was responsible for synthesizing input across all AMI members and making final decisions on content. This resulted in the loss of some individual perspectives and priorities on gap categorization. Focused on MI, this report does not comprehensively evaluate mAbs nor does it consider potential country preferences or differences in delivery between the two. Finally, this report is specific to maternal RSV vaccine, but many of the gaps identified, particularly in the delivery section, have implications much wider than a single vaccine. To fully evaluate the potential for RSV MI and enable valid comparisons with other vaccines and preventive strategies for LMICs, these additional elements will also need to be considered.

NEXT STEPS

This analysis presents an objective assessment of evidence and information essential to decision-making and/or introduction of RSV MI in LMICs identified by the AMI collaboration. Next steps for AMI include a formal ranking of the identified gaps by a broad group of experts both internal and external to AMI, representing the diverse immunization and MNCH communities to include researchers, implementers, governments, and donors. These findings will guide the development of a prioritized RSV MI roadmap. The roadmap will outline stage-appropriate activities to generate and assemble evidence and information to fill the gaps described in this report. It will also propose a timeline for conducting the work based on when the data are needed and how long it will take to generate. This roadmap will be updated annually as more evidence becomes available, gaps are filled, and/or new gaps are identified.
The AMI Secretariat welcomes input, which can be sent to AMISecretariat@path.org.

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6 APPENDICES

APPENDIX 1. LIST OF AMI MEMBERS

AMI Strategic Leadership	
Name	Title
Deborah Atherly	Global Head, Policy Access and Introduction, Center for Vaccine Innovation and Access, **PATH**
Theresa Diaz	Coordinator, Epidemiology, Monitoring and Evaluation (EME) team in Maternal and Newborn Child Health and Adolescent Health (MNCAH) at the **World Health Organization**
Cyril Engmann	Global Program Leader and Director for the Maternal, Newborn, Child Health and Nutrition (MNCHN) program, **PATH**
Joachim Hombach	Executive Secretary WHO SAGE; Senior Health Advisor, Initiative for Vaccine Research of the Department of Immunization, Vaccines, and Biologicals at the **World Health Organization**
Bruce Innis	Global Head, Respiratory Infections and Maternal immunization, Center for Vaccine Innovation and Access, **PATH**

AMI Technical Expert Panel	
Name	Title
Thomas Cherian	**WHO** Coordinator of EPI; former Coordinator for Implementation Research in the Initiative for Vaccine Research
Steve Hodgins	Associate Professor, **University of Alberta School of Public Health**, Global Health Program.
Raymond Hutubessy	Senior Health Economist, **WHO** Immunizations, Vaccines, and Biologicals
Philipp Lambach	Medical Officer, **WHO** Initiative for Vaccine Research
Matthews Mathai	Chair of MNCH at **Liverpool School of Tropical Medicine & Hygiene**
Claudia Morrissey Conlon	Senior Maternal and Newborn Health Advisor, **USAID**
Kate O'Brien	Executive Director, **Johns Hopkins International Vaccine Access Center**; Associate Director, Center for American Indian Health
Justin Ortiz	Associate Professor of Medicine, **University of Maryland Center for Vaccine Development**
Gloria Quansah Asare	Deputy Director-General, **Ghana Health Service**
Nathalie Roos	Program Officer, **WHO** Maternal, Newborn, Child, and Adolescent Health

AMI Secretariat	
Name	Title
Ranju Baral	Health Economist, Policy Access and Introduction, Center for Vaccine Innovation and Access, **PATH**
Jessica Fleming	Maternal Immunization Delivery Lead, Policy Access and Introduction, Center for Vaccine Innovation and Access, **PATH**
Devin Groman	Project Coordinator, Integrated Portfolio and Financial Management, Center for Vaccine Innovation and Access, **PATH**
Mark Gudmastad	Communications Officer, Policy Access and Introduction, Center for Vaccine Innovation and Access, **PATH**

Scott Haddock	Senior Project Manager, Integrated Portfolio and Financial Management, Center for Vaccine Innovation and Access, **PATH**
Deborah Higgins	RSV Vaccine Project Director, Respiratory Infections & Maternal Immunization, Center for Vaccine Innovation and Access, **PATH**
Kyla Jones	Program Assistant, Integrated Portfolio and Financial Management, Center for Vaccine Innovation and Access, **PATH**
Sadaf Khan	Senior Program Officer, Maternal, Newborn, Child Health & Nutrition, Global Health Programs, **PATH**
Bill Letson	Scientific Advisor, Policy Access and Introduction, Center for Vaccine Innovation and Access, **PATH**
Lauren Newhouse	Senior Communications Officer, Policy Access and Introduction, Center for Vaccine Innovation and Access, **PATH**
Clint Pecenka	Director of Health Economics and Outcomes Research, Policy Access and Introduction, Center for Vaccine Innovation and Access, **PATH**
Evan Simpson	Senior Program Officer, Policy Access and Introduction, Center for Vaccine Innovation and Access, **PATH**

AMI Disease Working Group Members

Name	Title
Naor Bar-Zeev	Pediatrics/Epidemiology **Johns Hopkins Bloomberg School of Public Health**; Wellcome Trust, **University of Malawi**
Abdoulreza Esteghamati	Head, **Pediatric Infectious Disease Research Center**, Iran; Member of National Immunization Technical Advisory Group
Barney Graham	Senior Investigator, Viral Pathogenesis Laboratory, **US National Institutes of Health**
Bernard Gonik	**USAID Jefferson Fellow**; Professor and Chair of Perinatal Medicine, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, **Wayne State University School of Medicine**
Ruth Karron	Professor, International Health, **Johns Hopkins Bloomberg School of Public Health**, Director of the Center for Immunization Research; Founding Director of the Johns Hopkins Vaccine Initiative
James Nokes	Professor, Infectious Disease & Epidemiology, **University of Warwick**, UK; Principal investigator, KEMRI Wellcome Trust
Ting Shi	Epidemiologist, **University of Edinburgh**
Rosalyn Singleton	Research Physician, **Alaska Native Tribal Health Consortium**; Guest researcher **Artic Investigations Program-CDC**

AMI Product Working Group Members

Name	Title
Mauricio Caballero	Clinical Researcher, **Fundación Infant**
Beate Kampmann	Professor of Paediatric Infection, Immunity and International Child Health, **Imperial College London**; Head - Vaccines and Immunity, MRC Gambia; IMPRINT network
Ruth Karron	Professor, International Health, **Johns Hopkins Bloomberg School of Public Health**, Director of the Center for Immunization Research; Founding Director of the Johns Hopkins Vaccine Initiative
Ben Lindsey	Clinical Research Fellow, **Imperial College London**
Jim Litch	Executive Director, **GAPPS**
Melissa Malhame	Consultant, former head of Market Shaping at **Gavi**
Renato Stein	Head, Pediatric Respiratory Service, School of Medicine; Director, Graduate Program on Child Health, **Pontifícia Universidade Católica do RGS**
Maria Stepanchak	Program Officer, **GAPPS**

AMI Health Economics & Financing Working Group Members

Name	Title
Taiwo Abimbola	Health Economist, **CDC**
Ranju Baral	Health Economist, **PATH**
Philippe Beutels	Health Economist, **University of Antwerp**
Raymond Hutubessy	Senior Health Economist, Immunizations, Vaccines, and Biologicals, **World Health Organization**
Mark Jit	Professor, Modeller, **London School of Hygiene and Tropical Medicine**
Ann Levin	Health Economist, **Consultant**
Carol Levin	Health Economist, **University of Washington**
Shanshan Zhang	Health Economist, **University of Edinburgh**

AMI Delivery Working Group Members

Name	Title
Nedghie Adrien	Epidemiologist, **CDC**
Teresa Aguado	Senior Advisor, **Barcelona Institute for Global Health**. Former coordinator at IVR, WHO
Azucena Bardají	Assistant Research Professor, **Barcelona Institute for Global Health**
Himanshu Bhushan	Advisor and Head of the Public Health Administration division of the **National Health Systems Resource Centre, India**
Leora Feldstein	Epidemiologist, **CDC**
Justus Hofmeyr	Director, Effective Care Research Unit. **Eastern Cape, South Africa, Department of Public Health**
Terri Hyde	Epidemiologist, **CDC**; Team Lead Vaccine Introduction Global Immunization Division; Immunization Systems Branch
Philipp Lambach	Medical Officer, **WHO** Initiative for Vaccine Research
Rebecca Levine	**USAID**, Maternal Health Technical Advisor
Sandra Mounier-Jack	Associate Professor in Health Policy - Vaccine delivery, **London School of Hygiene and Tropical Medicine**
Saad Omer	Global Health, Epidemiology, and Pediatrics Professor; **Emory University**
Azhar Abid Raza	Immunization Specialist, **UNICEF**
Nathalie Roos	Program Officer, **WHO** Maternal, Newborn, Child and Adolescent Health
Lauren Schwartz	Research Consultant, Epidemiology candidate at the **University of Washington**
Lora Shimp	Senior Immunization Technical Officer and Technical Lead, **John Snow Inc**
Peter Waiswa	Associate Professor at **Makerere University School of Public Health**; Visiting researcher at **Karolinska Institutet**, Sweden

APPENDIX 2. RSV MATERNAL IMMUNIZATION KEY QUESTIONS

Key questions for decision-making, rapid launch, and/or uptake in low- and middle-income countries

1. Epidemiological features of RSV
1.1 What is the incidence and mortality of RSV disease during the first year of life?
1.2 What are the national seasonal patterns of RSV in LMICs?
1.3 What are the transmission dynamics of RSV that result in infection of neonates and infants?
1.4 Is the distribution of RSV serogroups or serotypes associated with disease severity?
1.5 Does prevalence of severe disease in infants vary between populations with high coverage versus low coverage or absence of use of PCV/ influenza vaccine?
1.6 What are the predictors of mortality associated with RSV infection?
1.7 What is the burden of RSV in pregnant women by gestational age and the burden of RSV in post-partum women?
2. Clinical characteristics of RSV
2.1 What are the clinical features of RSV infection and disease in neonates (0-27 d) and infants (28d-11mo)?
2.2 How is RSV infection in neonates and infants diagnosed and clinically managed?
2.3 Are there long-term medical impacts of RSV disease in early life?
3. Other options for control and prevention of RSV
3.1 What options are currently available to prevent RSV disease in neonates and infants?
3.2 What new options to prevent RSV disease in neonates and infants are in development?
4. Vaccine characteristics
4.1 Which pregnant women should receive the vaccine?
4.2 What is the ideal dosing schedule of the vaccine?
4.3 What is the immunogenicity, efficacy, effectiveness, and impact of the vaccine?
4.4 Can the vaccine be co-administered with other vaccines recommended for use in pregnancy?
4.5 What is the duration of protection in infants born to immunized mothers? Against what endpoint and in what populations?
4.6 Is there evidence to support establishing a correlate of protection for RSV?
4.7 What affects maternal antibody transfer to the infant?
4.8 Are there risk factors in the mother for adverse outcomes in the pregnant mother and/or the infant following RSV immunization?
4.9 Is there evidence that the vaccine presents safety concerns in mothers, fetuses, neonates, and infants?
4.10 Where do active pharmacovigilance surveillance systems exist in LMICs?
4.11 Are there any indirect effects of the vaccine?
4.12 When will the vaccine be available for use in the first LMIC?
5. Economic considerations
a. Cost of illness
5.1 What is the economic burden of RSV?
5.2 What are the direct costs of RSV, including acute illness and potential sequelae for both providers and households?
5.3 What are the indirect costs of RSV (i.e. productivity costs)?

5.4 What fraction of cases lead to catastrophic health expenditures?
5.5 How do households pay for care?
5.6 Are loans a common source of financing as they often can lead to escalating costs?
5.7 What is the estimated benefit of an RSV intervention in terms of reducing antibiotic use and antimicrobial resistance (inpatient and outpatient)?
5.8 Can pneumonia or other respiratory illness cost data be used as a proxy for RSV? What adjustments and justifications does this require?
b. Cost of delivery
5.9 What are the vaccine delivery costs for both maternal immunization and mAb (e.g., communication and social mobilization for non-traditional populations, health worker training, additional health workers, integrating cold chain/logistics between EPI and ANC)?
5.10 Are vaccine delivery cost estimates realistic in that they account for poorly functioning ANC systems in some settings?
5.11 Can other delivery cost data be used as a proxy for maternal immunization or mAb? What adjustments and justifications does this require?
5.12 What information is available on the costs of integrating maternal immunization or mAb with other services?
5.13 Are there other examples of the cost of integrated programming that can serve as examples?
5.14 Assuming delivery cost data is not sufficient, how should this gap be filled? I.e. Should this be costing to inform benchmark MI or mAb costs, benchmark program integration or programmatic costing to inform country budgets and planning?
c. Demand impact and cost-effectiveness
5.15 What is the impact and cost-effectiveness of a maternal vaccine in a year-round delivery scenario vs. a seasonal delivery scenario?
5.16 What is the impact and cost-effectiveness of a monoclonal antibody in a year-round delivery scenario vs. a seasonal delivery scenario?
5.17 What is the incremental benefit of both interventions?
5.18 What would be the expected coverage with vaccination versus mAb?
5.19 What is the impact and cost-effectiveness of mAb for general populations and high-risk populations?
5.20 What is the full value of the vaccine? I.e. What is the cost-benefit ratio rather than a more narrow cost-effectiveness ratio?
5.21 Will either intervention improve health or economic equity or both?
5.22 Will either intervention reduce cases of poverty?
5.23 Will either intervention increase educational outcomes?
5.24 What is the market for the vaccine?
5.25 What is known about country interest and demand for the vaccine?
5.26 What is the estimated demand for the intervention in aggregate and by country?
5.27 What are the likely introduction dates/scenarios/timelines of the vaccine by country?
5.28 What is annual demand for each intervention stratified by income strata, Gavi status, other vaccines in the portfolio, MNTE status, region, wealth quintiles, mortality strata, cost-effectiveness, affordability, acceptability and feasibility?
5.29 What intervention (i.e. vaccine or mAb) is likely to be preferred by country? Which countries would consider introducing both interventions? Why and how?
5.30 What are the primary/critical uncertainties in demand, impact, and cost-effectiveness models/inputs that should be highlighted?
5.31 How might increased demand for ANC services due to maternal immunization enhance (or limit) the broader value of maternal immunization?
5.32 Is there any evidence that RSV MI would positively influence maternal health?
5.33 What are the opportunity costs of either intervention?
5.34 What are the other areas being highlighted for increased attention and funding in the MH field, e.g. diabetes, other NCDs and how will the RSV vaccine compete for funding and attention in this arena?

5.35 How does the disease burden, cost, and cost-effectiveness of RSV and the proposed RSV immunization intervention compare to these other areas identified for increased attention?
5.36 Will RSV interventions be compared to other MH interventions? Should they?
d. Financing and budget impact
5.37 What are the sources and levels of financing available for the vaccine?
5.38 How does this vaccine add to the burden of countries with Gavi having difficulty getting countries to pay for the vaccines they already procure and use?
5.39 Can countries afford the vaccines they already use?
5.40 What sources of funding are available, including non-traditional funding sources?
5.41 What financing instruments are possible or being discussed?
5.42 How might Gavi policies (e.g. graduation) change over time and what impact might this have on country co-financing options or demand in the future?
5.43 What resources do countries currently use including domestic resources and Gavi?
5.44 What is the affordability of the vaccine at the country level in LMICs?
e. Other
5.45 What information exists on intervention pricing (in low-, middle- and high-income countries) and/or the action of the intervention (including COGS)?
6. RSV vaccine delivery issues, including health systems considerations
a. Program issues/integration
6.1 What are the programmatic issues and challenges around introduction of this vaccine, particularly when considering integrating RSV vaccine delivery into the ANC platform?
6.2 What are the challenges and/or opportunities of the new WHO ANC recommendations in relation to integrating the vaccine into existing services?
6.3 What, if any, supplemental benefits are expected with introduction of the intervention in relation to ANC uptake and/or newborn delivery care?
6.4 What are the preferred strategies (integration into ANC, EPI, vaccination campaigns, outreach services) to reach the target population with the intervention in relation to the existing health system?
6.5 What are the lessons from other efforts around integration of vertical programs into maternal health services?
6.6 What are the possible effect of the introduction of the vaccine on the wider health system?
b. Logistics
6.7 What are the cold chain and logistical requirements for the vaccine?
6.8 How would the logistics of a maternal vaccine provided through ANC be managed and by whom?
c. Acceptability
6.9 What is the acceptability of the vaccine among key populations, including professional organizations, health care providers and pregnant women?
6.10 Would stakeholders be expected to have a preference for one RSV intervention (maternal immunization or mAbs) over the other?
6.11 What are the factors associated with vaccine acceptance and hesitancy?
6.12 What are the geographic, cultural, and economic barriers to accessing health care, especially in pregnancy?
6.13 What mechanisms exist to identify families without access to routine health facilities/services?
6.14 What factors would support the sustainability of procuring/providing the vaccine?

d. Monitoring & evaluation
6.15 How is the target population for the intervention identified and tracked?
6.16 How is ANC care-seeking and vaccination receipt tracked in pregnant women?
6.17 What systems are in place to monitor the impact of the intervention?
6.18 What data and monitoring mechanisms exist around pregnancy and newborn outcomes?
6.19 What mechanisms exist that monitor and assess child health outcomes during the neonatal period and beyond?
6.20 What are the training level and credentials of MCH and field staff typically reporting AEFIs and other birth outcomes in LMICs?
e. Policy
6.21 What is the degree of existing awareness of/buy-in to MI among the various people and organizations that must be involved in bringing a maternal RSV vaccine to market/introduce in LMICs?
6.22 What existing global, regional, and country policies might enable and/or inhibit uptake of maternal RSV vaccines?
6.23 Who needs to be engaged at the global, regional, national, and sub-national levels to move RSV maternal immunization forward?
7. Social impacts
7.1 What is the possible impact of RSV MI on social equity and equality?
7.2 What gender and cultural issues potentially affect the successful introduction and use of the vaccine?
8. Legal considerations
8.1 What are the legal requirements for implementing RSV vaccination?
8.2 What legal issues related to AEFIs may influence the decision to introduce or successfully implement the intervention?
9. Ethical considerations
9.1 Are there ethical considerations for providing a vaccine that mainly benefits the infant and not the mother herself?

APPENDIX 3. AMI GAP ANALYSIS FRAMEWORK TEMPLATE

Key Question:

Address the following in your evidence review:

Question Lead:	Question researcher (s) (if applicable)

List individuals who provided expert opinion, advice, or review in filling out the framework below (include name and organization):

1. What information currently exists relative to this question that supports efficient, well-informed decision-making or supports effective launch and uptake of RSV maternal immunization in low and middle-income countries (LMICs)? Please succinctly describe the available evidence, actions and/or environment as appropriate, and cite your sources, as applicable (include source/citation; if journal article, include first author, name of journal, year of publication, and title).

❑ Check the box if no information currently exists.

2. Based on your review of the existing information, indicate the degree to which the evidence, actions, and/or environment are sufficient for decision-making or effective launch and uptake of RSV maternal immunization in LMICs by checking one of the boxes below.

[NOTE: Please consider the following when making your selection: (1) Nature of evidence; (2) Generalizability; (3) Context and location; (4) Consistency; (5) Overall quality; and (7) Limitations and biases.]

Evidence needs, actions, and/or supportive environment for decision-making or effective launch and uptake are:

❑ Sufficiently met* *Skip to Section 4.

❑ Insufficiently or not met** **If you check this option, please complete the Gap Analysis Table in Section 3.

❑ Not Applicable* *Skip to Section 4.

3. Gap Analysis Table

In the following table, please list the gaps in evidence, actions, and/or environment and elaborate on needs that would support decision-making or effective launch and uptake of RSV maternal immunization in LMICs.

Identify gap.	What are the reasons for the gap?	What are the opportunities/solutions to fill the gap and who needs to be involved?	What decisions require this information?	List any relevant ongoing efforts, activities, or initiatives that could contribute to filling the gap and identify key contacts.
List gaps **critical** for decision-making or effective launch and uptake. One gap per row.	List reasons, if known.	List opportunities/ solutions and identify general categories of stakeholders that need to be involved in the efforts (e.g., researchers, health practitioners, funders, advocates, global or country policymakers, etc.)	For example, will Gavi need this information to make vaccine investment decisions? WHO for vaccine PQ or policy recommendations? Country ministries of health for introduction decision-making or implementation?	List organization, project name/ initiative, funder, and timeline (if known). List names and emails of key contacts.

4. Please use the space below to provide any additional information or comments.

APPENDIX 4. RSV MATERNAL IMMUNIZATION GAPS

The table herein is the comprehensive list of all of the gaps identified by the AMI Working Groups (WGs) through the Respiratory syncytial virus (RSV) maternal immunization gap analysis. This includes gaps categorized as "essential but peripheral", which were not included in the main report. For ease, the list is organized by six topic areas: Epidemiology, Vaccine and Immunization Characteristics, Health Economics and Financing, Programmatic Considerations, Policy and Advocacy, and Monitoring and Safety Surveillance. These topic areas are based on the major categories used to display evidence for the development of the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) recommendations on immunization. In certain cases, multiple WGs identified similar gaps within their purviews. To reduce redundancy, duplicative gaps are only included once and are listed as essential, as all were categorized as such by at least one WG.

Gap categories and their definitions:

- *Essential and specific to maternal immunization*: A gap in information or conditions that is unique to MI and that MUST be addressed for MI decision-making, launch, and/or uptake to move forward
- *Essential across immunizations*: A gap in information or conditions that is generally applicable across vaccines and that MUST be addressed for MI decision-making, launch, and/or uptake to move forward
- *Non-essential but supportive*: A gap in information or conditions that, if addressed, could strengthen or accelerate MI decision-making, launch, and/or uptake, but is not required to move forward
- *Non-essential and peripheral*: A gap in information or conditions that may be of interest, but does not need to be addressed to advance, strengthen, or accelerate MI decision-making, launch, and/or uptake

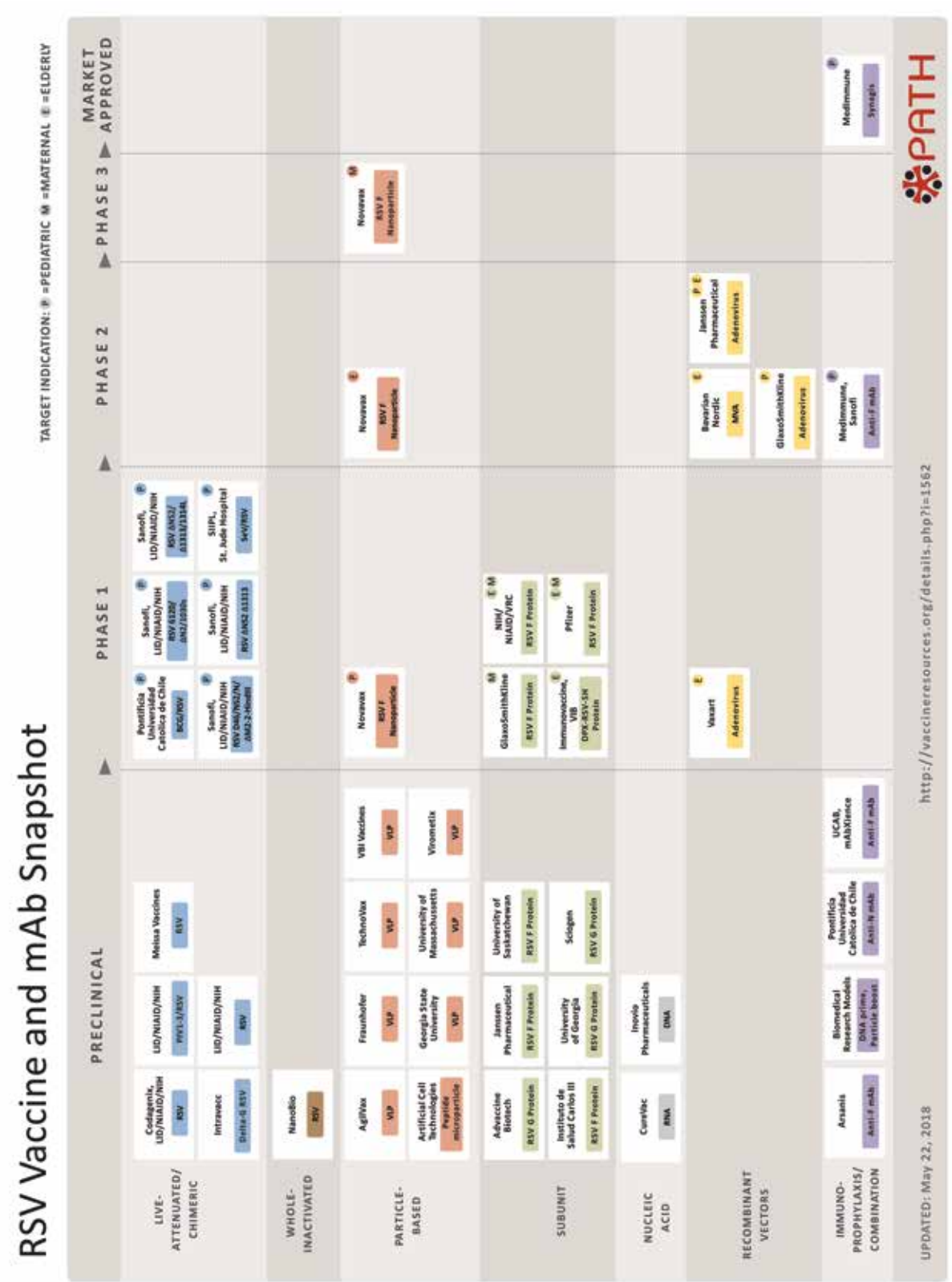
	Epidemiology	Vaccine/ Immunization Characteristics	Health Economics and Financing	Programmatic Considerations	Policy and Advocacy	Monitoring and Safety Surveillance
Essential and specific to maternal immunization	❑ RSV burden of disease data stratified by narrow age bands for infants and collected in 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.	❑ 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. ❑ Additional data on the effect of maternal co-morbidities and preterm labor on RSV vaccine immunogenicity, maternal antibody transfer, and vaccine effectiveness. ❑ 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. ❑ 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.	❑ 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. ❑ 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.	❑ Information and data across settings on current mechanisms and modalities for ANC delivery and their capacity to routinely deliver vaccines. ❑ 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. ❑ Defining cold chain, logistical, and vaccine management requirements and processes for maternal RSV vaccines. ❑ Data on the impact of integrating RSV MI with existing ANC services on ANC quality and coverage.	❑ Understanding the drivers and barriers for RSV MI acceptance and uptake in LMIC contexts. ❑ 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. ❑ Information on RSV disease and MI to support stakeholder awareness, engagement, and advocacy at regional and country levels.	❑ 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. ❑ Strengthened immunization monitoring and surveillance systems in LMICs to reliably track and report pregnancy and birth outcomes, vaccine coverage, and AEFIs. ❑ Background rates on pregnancy outcomes in LMICs to facilitate maternal RSV vaccine safety data interpretation.

	Epidemiology	Vaccine/ Immunization Characteristics	Health Economics and Financing	Programmatic Considerations	Policy and Advocacy	Monitoring and Safety Surveillance
Essential across immunizations	❑ Collection of standardized data, including continuous variables, to allow comparison across studies regardless of case definition. ❑ 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.	❑ Greater precision around the timing of RSV intervention licensure and WHO prequalification to improve estimates of intervention availability in LMICs. ❑ No WHO prequalified maternal RSV vaccine currently exists.	❑ Funding support for RSV vaccine identified for Gavi-eligible and non-eligible LMICs. ❑ 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. ❑ 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. ❑ 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. ❑ 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. ❑ Clarity around Gavi-eligible and non-Gavi eligible countries' ability to afford the vaccines in their current portfolio.	❑ The WHO Effective Vaccine Management assessment tool does not include maternal RSV vaccine delivery and management assessment variables. ❑ A technical field manual on maternal RSV vaccine introduction for LMICs.	*No gaps identified in this category.*	*No gaps identified in this category.*

	Epidemiology	Vaccine/ Immunization Characteristics	Health Economics and Financing	Programmatic Considerations	Policy and Advocacy	Monitoring and Safety Surveillance
Non-essential but supportive	❑ Data on the seasonal distribution of RSV in LMICs to inform optimal vaccine delivery strategies. ❑ Additional evidence from LMICs on RSV seasonal variation, annual variation in disease incidence, transmission dynamics, RSV serogroup prevalence, and clinical treatment management standards. ❑ Evidence on effect of pneumococcal and influenza immunizations on RSV disease patterns, including the proportion of bronchiolitis and other acute lower-respiratory illness (ALRI) attributed to RSV. ❑ Data on RSV disease burden in specific sub-populations to inform appropriate vaccination strategies for high-risk populations. ❑ Additional evidence on RSV burden in pregnant women.	❑ Evidence of maternal vaccine effect against RSV infection in infants. ❑ 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. ❑ 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. ❑ Standardized immune assays or harmonized assay data using appropriate international reference standards to allow comparison across studies and vaccine candidates. ❑ Disease models to predict the effectiveness of maternal RSV vaccines. Data on the level and duration of vaccine-induced and naturally derived maternal RSV antibody can be used to model the relationship between maternal RSV antibody levels in serum and breast milk and duration of protection from RSV disease and infection in infants' first few months of life. ❑ When pediatric RSV vaccines become available, evaluation of interference of vaccine-induced maternal RSV antibody on active immunization of infants against RSV.	❑ Information about the costs associated with potential RSV disease sequelae (e.g., wheeze and asthma), which is important assuming evidence of causality. The extent to which this information is useful for LMICs, however, is unknown because the burden may be underappreciated, and treatment may not be common. ❑ 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. ❑ Evidence on effective strategies to enhance impact and cost-effectiveness of RSV interventions in LMICs.	❑ 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. ❑ Information on effective mechanisms for following up with women that miss visits or do not seek ANC in LMICs. ❑ Strategies to improve vaccination coverage in women who do and do not receive ANC via the formal healthcare system, including missed vaccination opportunities.	❑ 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. ❑ Additional evidence on appropriate framing and messaging of RSV MI for different stakeholder groups. ❑ Incorporating women's perspectives into vaccine development and introduction planning—both as policy makers and end-beneficiaries. ❑ Despite international standards, national regulatory authorities in LMICs generally lack the legal authority to enforce adverse event reporting requirements.	*No gaps identified in this category.*

	Epidemiology	Vaccine/ Immunization Characteristics	Health Economics and Financing	Programmatic Considerations	Policy and Advocacy	Monitoring and Safety Surveillance
Non-essential and peripheral	❑ The impact of pneumococcal conjugate vaccine on ALRI disease occurrence varies by country, making the relationship of RSV and prevention of pneumococcal disease difficult to define in terms of possible secondary effects of a maternal RSV vaccine. ❑ Evidence on whether vertical transmission of RSV impacts wheezing illness in infants, the prevention of which would be a secondary impact of maternal RSV immunization.	*No gaps identified in this category.*	❑ Additional information around the potential financial consequences of implementing the new WHO ANC guidelines for women and their families, including whether or not higher costs would lead to lower ANC attendance.	❑ Documentation of effective vaccine delivery platforms and strategies, and the pros and cons of alternatives. ❑ Mechanisms for collecting data and information on the supplemental benefits of maternal RSV immunization on maternal and newborn health, including service uptake along the continuum of care. ❑ Additional data on the availability and quality of sonography in LMICs to identify background rates of adverse outcomes in pregnancy.	*No gaps identified in this category.*	❑ Consensus on a widely-acceptable definition of minimal risk in pregnancy.

APPENDIX 5. RSV VACCINE AND mAB SNAPSHOT



ami Advancing Maternal Immunization

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