WHO/IVB/17.12

RSV Vaccine Research and Development Technology ROADMAP

Priority activities for development, testing, licensure and global use of RSV vaccines, with a specific focus on the medical need for young children in low- and middle-income countries

2017

World Health Organization

RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINE TECHNOLOGY ROADMAP

This document was produced by the
Initiative for Vaccine Research (IVR)
of the Department of Immunization, Vaccines and Biologicals

Ordering code: WHO/IVB/17.12
Published: 2017

This publication is available on the Internet at:
http://www.who.int/immunization/documents/en/

Copies of this document as well as additional materials on immunization, vaccines and biologicals may be requested from:
World Health Organization
Department of Immunization, Vaccines and Biologicals
CH-1211 Geneva 27, Switzerland
• Fax: + 41 22 791 4227 • Email: vaccines@who.int •

Contents

Acknowledgments

This work was built on critical input from the WHO RSV Vaccine Technical Working Group members (Narendra Arora (INCLEN Trust International, New Delhi, India), Barney Graham (National Institute of Health, Bethesda, USA), Ruth Karron (John Hopkins Bloomberg School of Public Health, Baltimore, USA), David Kaslow (PATH, Seattle, USA), Peter Smith (London School of Hygiene and Tropical Medicine, London, UK)) as well as Kayvon Modjarrad (Walter Reed Army Institute of Research, USA). We are grateful to all individuals and represented institutions who attended a WHO consultation meeting on group RSV vaccine development on 25–26 April 2016 in Geneva and contributed to the discussions, and to the members of the WHO Product Development for Vaccines Advisory Committee (http://www.who.int/immunization/research/committees/pdvac). The document was available for public consultation during early 2017 and we are grateful to the individuals and institutions who provided feedback.

WHO secretariat

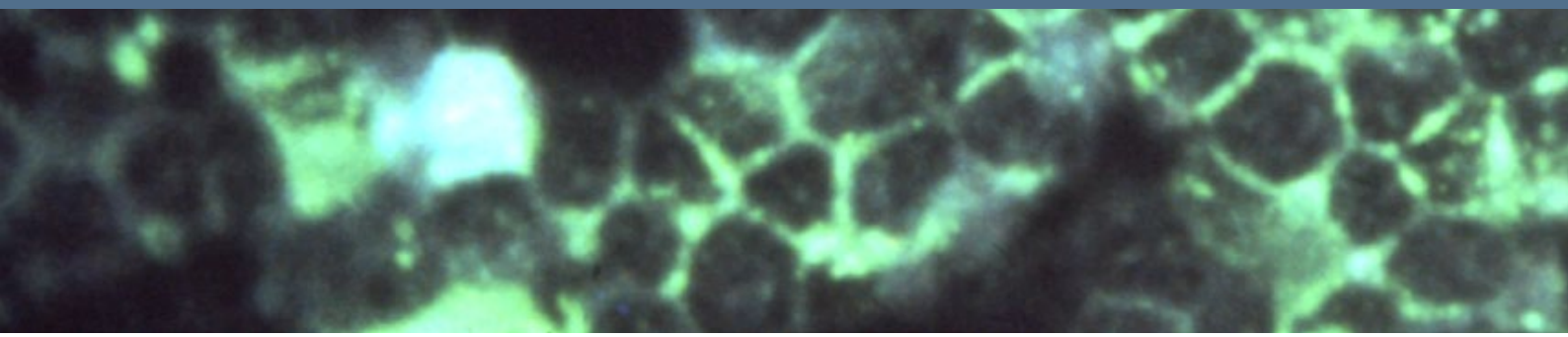
Martin Friede, Birgitte Giersing, Joachim Hombach, Vasee Moorthy, Johan Vekemans.

Funding

This work was supported by the Bill & Melinda Gates Foundation, Seattle, WA [Global Health Grant OPP1114766].

Credits

Page 3: CDC/Dr. Craig Lyerla
Page 4: CDC/Julia Whitney, Stephen Griffin
Page 5: WHO/TDR/Andy Craggs
Page 6: CDC/Douglas Jordan
Page 7: CDC
Page 8: CDC/Jessie Blount
Page 9: WHO/TDR/Simon Lim



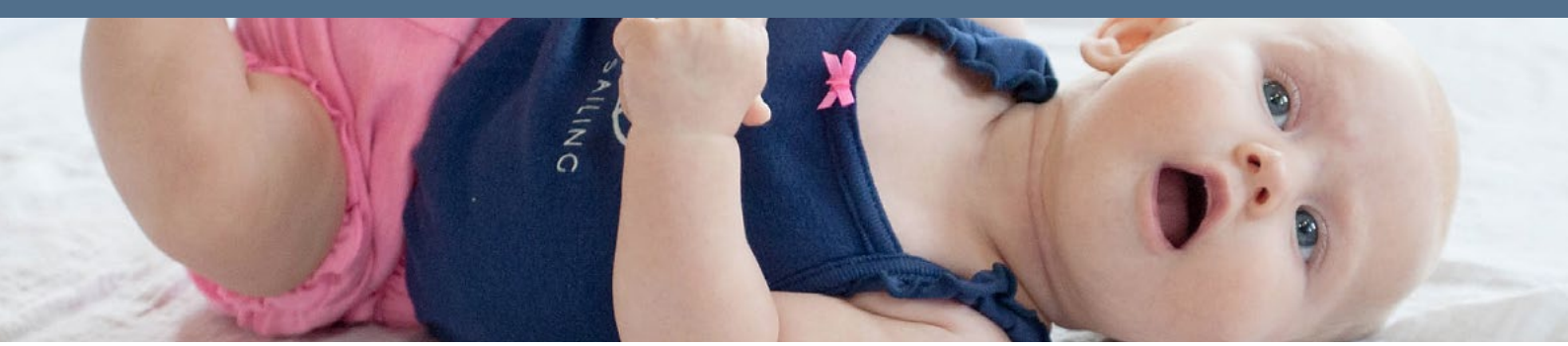
Background

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection in neonates and young infants. The risk of severe outcome is highest in the first months of life, but RSV causes significant morbidity throughout childhood. A vast majority of the disease burden lies in low- and middle-income countries (LMIC). Seasonal incidence variations are marked in temperate climates, more than in tropical areas. Important gaps in epidemiological characterisation remains, including data to define the long term impact of RSV infection on respiratory health.

Symptomatic supportive care constitutes the cornerstone of severe RSV disease clinical management. One licensed monoclonal antibody used for passive immunization is recommended and available for prevention of severe RSV in selected high-risk groups in high-income countries. However, this intervention is generally not accessible in lower resource settings due to its cost and monthly dosing delivery logistics. Second generation candidate monoclonal antibodies, with improved pharmacokinetics, pharmacodynamics and/or lower cost are being evaluated.

RSV vaccine research and development activities have been re-vitalised in the last years, as the field advanced beyond the legacy of enhanced RSV disease caused by immunization with crude formalin-inactivated whole virus vaccine in the 1960s. In March 2015 and April 2016, WHO convened consultations with RSV subject matter experts from academia, industry, government and regulatory authorities to formulate guidance on RSV vaccine development. The need to prepare in anticipation of RSV vaccine licensure in years ahead, to identify and address gaps in the pathway to prequalification, policy recommendation and implementation, was highlighted. Significant progress was made on developing strategic goals, drafting candidate case definitions, and identifying development pathways for RSV vaccines – particularly those administered through maternal immunization and targeting protection of young infants in the first months of life.

To ensure meaningful vaccine impact where it is most needed in the shortest timeframe possible, a number of key research and product development activities need to be undertaken. These priority activities are outlined in this document. Many activities presented here are relevant to the field of prophylactic monoclonal antibody development, and some specific needs to support the development of passive immuno-prophylaxis for use



in LMIC are highlighted herein, but more detailed priorities are beyond the scope of this document. While vaccine development activities targeting protection against RSV disease in the elderly are ongoing, this population is currently not prioritized within the scope of this document.

Outlined below, the RSV vaccine 'Vision' articulates the prioritized public health need and the 'Strategic Goals' describe two vaccination strategies designed to realize that vision.

Updates to this Roadmap will be formally considered following significant research findings, product development events, or changes to key underlying assumptions that warrant reassessing this stated vision, strategic goals or priority activities. WHO will encourage implementation of the finalised roadmap by the RSV vaccine community.

Vision

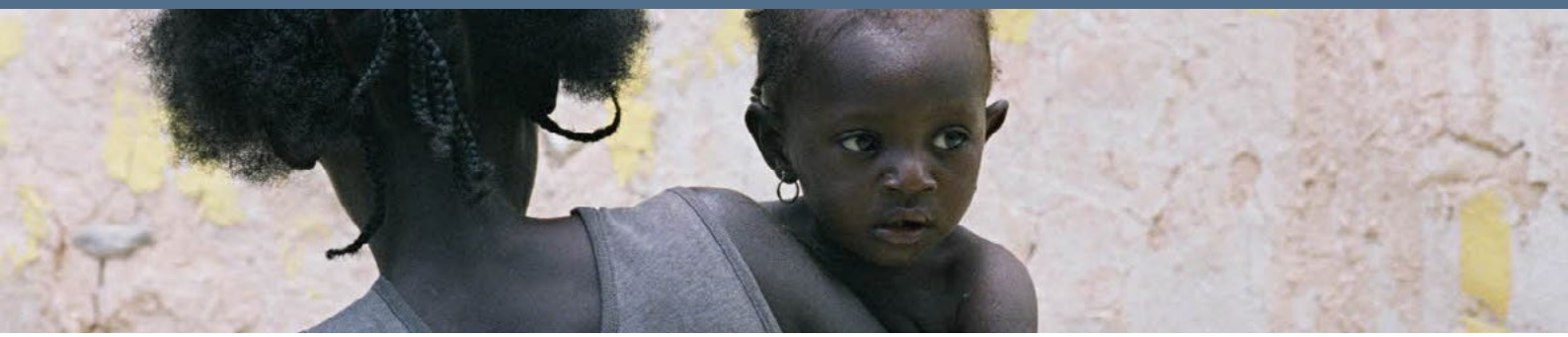
There is a need for high-quality, safe, effective, affordable and accessible RSV vaccines that prevent severe disease and death in infants less than 12 months of age and reduce morbidity in children less than 5 years of age, appropriate for use in LMICs.

Strategic Goals

Develop and license high-quality, safe and effective RSV vaccines that prevent severe disease and death in infants less than 12 months of age and to reduce morbidity in children less than 5 years of age, and to ensure they are available and affordable for global use including in LMICs.

Two priority approaches are identified:

1. Development of vaccines for maternal immunization during pregnancy leading to trans-placental antibody transfer and prevention of severe RSV disease in neonates and young infants.
2. Development of vaccines for paediatric immunization to prevent RSV disease in infants and young children.



Consensus priority activities

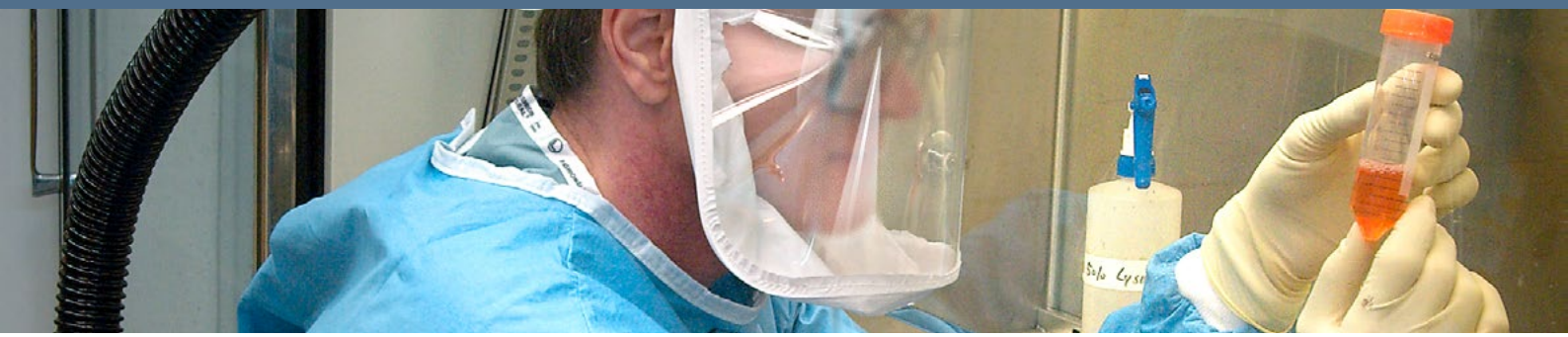
Research

Improve global estimates of disease burden and potential vaccine impact.

- Improve global RSV surveillance platforms and conduct epidemiology studies to generate estimates of age-stratified disease burden (especially in the first months of life) including mortality; identify risk factors (including co-infections) for adverse outcomes; clarify the relationship between RSV and recurrent wheezing, reactive airway disease and asthma; improve understanding of RSV transmission dynamics to identify potential target groups for prevention of transmission; describe local seasonality patterns to inform seasonal vs age-based vaccination strategies.
- Develop RSV disease burden (considering co-infections) and transmission mathematical models for further estimation of potential vaccine impact and selection of vaccine strategies and target population.
- Estimate the potential benefit of RSV vaccines in reducing antibiotic use and antimicrobial resistance.

Increase availability and quality standards of pre-clinical tools for evaluating candidate RSV vaccines.

- Better define the relevance of existing tools for preclinical safety and efficacy evaluation towards establishment of a consensus pre-clinical evaluation strategy and down-selection criteria for prioritization of vaccine candidates to progress to clinical evaluation.
- Ensure access to relevant preclinical tools and comparability of results between laboratories.



Develop quality-assured standard reference immune assays.

- Develop international reference standards to facilitate the comparison of immune responses to candidate RSV vaccines, including RSV-neutralizing antibody activity as measured by a variety of assays including plaque reduction neutralization, microneutralization, reporter virus, and epitope-specific assays.
- Establish accessible standard assay guidance and/or protocols to encourage harmonization and results comparability.

Vaccine development

Define key elements of clinical development progression steps and vaccine clinical trial design.

- Establish a consensus on staged clinical development plans for vaccine evaluation in pregnancy (maternal immunization) and RSV seronegative (previously unexposed) infants (pediatric immunization), minimizing exposure to a risk of post-vaccination enhanced disease caused by subsequent natural RSV infection.
- Define optimal dose, schedule, timing of vaccination during pregnancy and the need for re-vaccination during subsequent pregnancies (maternal immunization).
- Define safety and efficacy study endpoint case definitions and standard data capture methodologies relevant and applicable in LMICs, allowing comparisons across studies; define candidate case definition sensitivity and specificity. Incorporate collection of healthcare resource and antibiotic use data associated with RSV disease in pivotal efficacy studies.
- Define relevant immunological assays in clinical trials, with the goal of determining correlates of vaccine-induced protection.
- Determine an appropriate strategy for assessment of the long-term effects of vaccination on recurrent wheezing and reactive airway disease.

Ensure availability of key findings from clinical studies and publication of data and results within 12 and 24 months, respectively, of the last subject's last visit for the primary endpoint (refer to http://www.who.int/ictrp/results/reporting/ for further information on WHO data transparency initiative).

Key capacities

Establish manufacturing capacity to support global RSV vaccine cGMP manufacture for commercial production in line with future evidence-based demand predictions.

Strengthen GCP research capacity and preparedness for RSV vaccine trial conduct to include centres in LMICs.

- → Establish baseline rates of disease per relevant standard case definitions and data capture procedures; define local seasonal variations in incidence.
- → Establish baseline rates of common adverse pregnancy, birth, and neonatal outcomes to prepare for optimal safety data capture following maternal vaccination in pregnancy.

Support regulatory capacity-strengthening in LMICs for clinical trial authorisation and review of licensure applications; when relevant, vaccine developers should engage multi-national regulatory networks in LMICs for increased efficiency.

Determine regulatory approval and WHO prequalification pathway for long-acting monoclonal antibodies.

Policy and delivery

Establish health economic value proposition including cost effectiveness, with transparency on assumptions, data gaps, and underlying evidence needed to support appropriate financing and policy decision-making at the global and national level.

Develop functional RSV vaccine program delivery platforms.

- Identify health systems strengthening needs for potential integration of RSV vaccines in maternal and/or neonatal health programs, including antenatal care (ANC) and the Expanded Programme on Immunisation (EPI).
- Develop consensus on optimal vaccination schedules across regions considering seasonal incidence variations (i.e. seasonal vs age-determined vaccination).
- Identify appropriate delivery platform(s) for long-acting monoclonal antibodies.

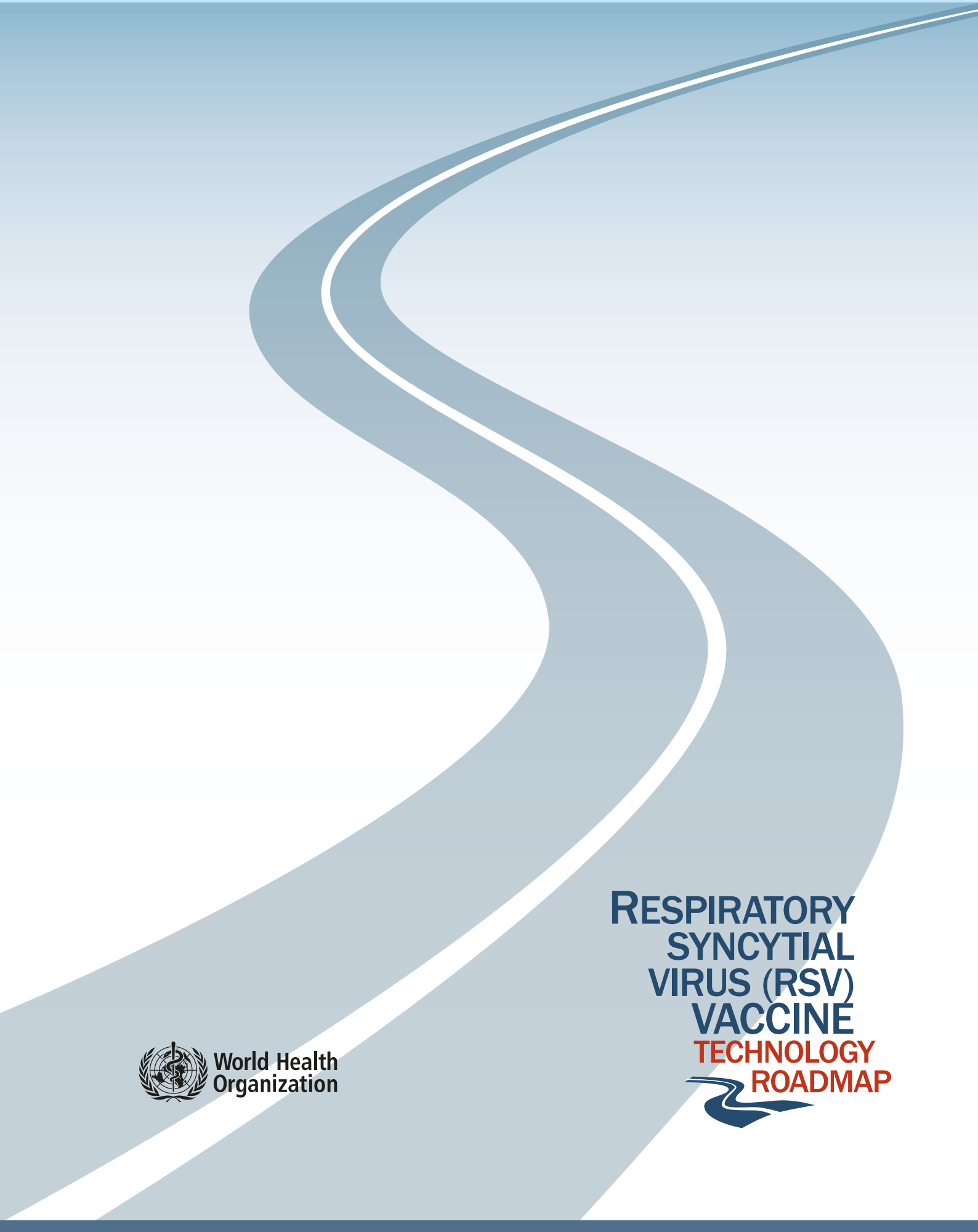
Develop and implement global, regional, and national advocacy and communication plans to strengthen awareness, mobilize resources and optimize vaccine uptake.

- Develop educational tools and appropriate messages related to RSV disease burden and the role of vaccination, to engage key audiences (which may include, but are not limited to, parents/care givers, clinicians, policy makers and advocates).
- Collaborate with other maternal vaccination efforts (targeting tetanus, influenza, pertussis, and Group B streptococcus) to proactively develop successful implementation strategies; identify and address potential barriers to vaccine access and uptake, taking into account health care provider's perspectives, community acceptance, and user concerns.

Develop post-implementation surveillance platforms to support research on vaccine effectiveness, pharmacovigilance, impact on health systems and antibiotic use, and the operational aspects of vaccination programs.


OLYMPUS

WHO/IVB/17.12



RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINE TECHNOLOGY ROADMAP

World Health Organization