Call for Proposals:
Methodological considerations for studies to measure the association between RSV LRTI and wheeze/asthma

1. Introduction:

The WHO Initiative for Vaccine Research\(^1\) is seeking proposals for the above mentioned work and as outlined in more detail below.

2. Background:

Respiratory Syncytial Virus (RSV) is the leading viral cause of lower respiratory tract infections (LRTI) worldwide. Recent modelling estimates suggested that in 2015 there were 33 million RSV LRTI cases worldwide and 118,000 deaths in children <5 years of age, mostly in developing countries. Approximately half of severe RSV disease occurs among infants <6 months of age. Besides the clear burden of acute RSV lung infection, there is evidence that RSV LRTI is associated with recurrent wheezing and asthma, and decreased lung function, later in childhood. The causal relationship between RSV LRTI in early childhood and later development of wheeze/asthma, however, has not been definitely shown. On the one hand, early RSV LRTI might permanently alter the lung’s physiologic and immunologic development causing subsequent wheeze/asthma. On the other hand, a child’s predisposition to wheeze might itself lead to greater severity of disease in the setting of RSV infection. Alternatively, children who are predisposed to have severe RSV-associated LRTI might also be predisposed, independently, to get recurrent wheezing/asthma throughout childhood. Which of these scenarios is true can have important implications on the long-term impact of RSV vaccines and other preventive products.

The scientific literature presents contradictory results in defining the association between RSV-associated LRTI and recurrent wheeze/asthma. A recent systematic review of the literature found 74 studies with relevant data (Fauroux B, Infect Dis Ther 2017). The authors conclude that the majority of studies showed a positive association between early RSV LRTI and recurrent wheeze/asthma. Some studies noted a transient association between RSV LRTI and wheeze (up to a year of age), while in others the association persisted into young adulthood. The authors also point out that there was substantial heterogeneity in the study design, patient populations studied, the classification of RSV LRTI, the length of follow-up, the definitions of wheeze and asthma, and the rates of wheeze/asthma in the populations. Moreover, the review showed that studies in certain subgroups found variable associations, suggesting potential confounders or effect modifiers, of the RSV-wheeze association (e.g., prematurity, underlying conditions, household air pollution, exposure to tobacco smoke.) Additional data informing the association between RSV and wheeze/asthma are available from two randomized controlled trials of monoclonal antibodies that prevent RSV LRTI in infants. One study among Dutch healthy, premature infant evaluated the impact palivizumab on recurrent wheezing. The study found that wheeze days, as defined by parental report, were decreased in the first year of life among palivizumab recipients (Blanken MO, N Engl J Med 2013; Scheltema NM, Lancet Respir Med 2018). Longer term follow-up of a

\(^1\) IVR’s mission is to guide, provide vision, enable, support, and facilitate the development, clinical evaluation and worldwide access to safe, effective and affordable vaccines against infectious diseases of public health importance, especially in developing countries. See also, [http://www.who.int/immunization/research/en/](http://www.who.int/immunization/research/en/)
subset of study participants until 6 years of age demonstrated a decrease in parental report of mild asthma among palivizumab recipients, but no difference in physician-diagnosed asthma or lung function testing evidence of airway obstruction. The second RCT used motavizamab in full-term Native American infants, who were followed up to three years of age (O’Brien KL, Lancet Infect Dis 2015). The investigators found no difference in medically-attended wheeze between the study groups.

The reasons for the variable findings on the association between RSV LRTI and wheeze/asthma are not clear. It is possible that the association could be present or stronger in some populations of children, and the study heterogeneity reflects the epidemiology. However, it is also possible that methodological issues could produce different results, and/or lead to potential bias affecting the results. Among some of these methodological differences are how the outcome of wheeze/asthma was measured, the time period of follow-up, whether the design was a cohort study or RCT, and the sample size of the studied populations. To accurately measure the association between RSV LRTI and wheeze/asthma, it is essential to implement methodologies that minimize bias.

3. **Purpose and objectives:**

WHO is requesting a scope of work that addresses this question of methodological considerations in the measurement of this association. As part of the work we expect the grantee to address the following:

- Define the methodological differences in study design.
- Explain how different methodologies can lead to different results.
- Describe how the findings might differ in important high-risk populations (e.g., premature infants) and if there are unique methodological issues in these sub-groups.
- Make recommendations for study designs and methods in the future to best elucidate the association of RSV and wheeze/asthma.

4. **Deliverables:**

The anticipated deliverables of this work will be the following:

- A report to WHO on methodological considerations by 15 October 2018.
- Preparation with contribution from WHO a journal article based on the report.
- Submit for publication in an open access peer-reviewed journal (WHO will take care of open access fees and license agreement separately) by Q1 2019.
- A presentation at a WHO-organized meeting on measuring the longer-term impact of RSV vaccines, tentatively scheduled for Q4 2018.

While knowledge of relevant literature will be necessary, it is not expected that this will be a systematic review of the literature on this topic. Key studies should be included to demonstrate the points; however, a comprehensive catalogue of studies is not necessary.

5. **Proposal submission:**

The following information should be included within the submission (maximum of 3 pages):

- Contact information for your organization.
- Description of approach and timelines for project.
- General information about the planned research team, including roles and responsibilities on this project.
- Proposed budget.

Please also attach to the proposal:
- CVs of the proposed research team.
- Declaration of conflicts of interest for all named persons on the research team (with WHO disclosure form).

Proposals must be submitted by email to feikind@who.int and sparrowe@who.int. The electronic submission has been extended (from 31 May 2018) and must be received by 10 June 2018 and should include “Methodological considerations for studies to measure the association between RSV LRTI and wheeze/asthma” in the subject line.

6. Evaluation criteria:

The successful proposal will be selected on the basis of:
- Experience of the principal investigator and the team’s expertise conducting and disseminating similar research.
- Methodological rigor of their proposed approach, including feasibility of timelines.
- Proposed timelines and likelihood to meet deadlines.
- Proposed budget/overall value of the project.

Applicants are expected to disclose any possible conflict of interest capable of influencing their judgments, including personal, political, proprietary, family, academic and financial. A WHO disclosure form for Declaration of Interest must be completed by all named persons on the research team and submitted with the RFP application. Upon receipt, IVR staff will screen all applications for completeness and for compliance with the parameters of this competition. IVR staff will rank complete and compliant applications based on the mentioned evaluation criteria. Final authority on funding approval rests with the WHO Secretariat. WHO will notify the successful applicants directly. WHO is unable to provide individual feedback on unsuccessful applications.