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

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\(^1\) 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 motavizumab 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 must be received by 31 May 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.
DECLARATION OF INTERESTS FOR WHO EXPERTS

WHO's work on global health issues requires the assistance of external experts who may have interests related to their expertise. To ensure the highest integrity and public confidence in its activities, WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to a potential conflict of interest related to the subject of the activity in which they will be involved.

All experts serving in an advisory role must disclose any circumstances that could represent a potential conflict of interest (i.e., any interest that may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). You must disclose on this Declaration of Interests (DOI) form any financial, professional or other interest relevant to the subject of the work or meeting in which you have been asked to participate in or contribute towards and any interest that could be affected by the outcome of the meeting or work. You must also declare relevant interests of your immediate family members (see definition below) and, if you are aware of it, relevant interests of other parties with whom you have substantial common interests and which may be perceived as unduly influencing your judgement (e.g. employer, close professional associates, administrative unit or department). Please note that not fully completing and disclosing all relevant information on this form may, depending on the circumstances, lead WHO to decide not to appoint you to WHO advisory bodies/functions in the future.

Please complete this form and submit it to WHO Secretariat if possible at least 4 weeks but no later than 2 weeks before the meeting or work. You must also promptly inform the Secretariat if there is any change in this information prior to, or during the course of, the meeting or work. All experts must complete this form before participation in a WHO activity can be confirmed. Please note that not fully completing and disclosing all relevant information on this form may, depending on the circumstances, lead WHO to decide not to appoint you to WHO advisory bodies/functions in the future.

Answering "Yes" to a question on this form does not automatically disqualify you or limit your participation in a WHO activity. Your answers will be reviewed by the Secretariat to determine whether you have a conflict of interest relevant to the subject at hand. One of the outcomes listed in the next paragraph can occur depending on the circumstances (e.g, nature and magnitude of the interest, timeframe and duration of the interest).

The Secretariat may conclude that no potential conflict exists or that the interest is irrelevant or insignificant. If, however, a declared interest is determined to be potentially or clearly significant, one or more of the following three measures for managing the conflict of interest may be applied. The Secretariat (i) allows full participation, with public disclosure of your interest; (ii) mandates partial exclusion (i.e., you will be excluded from that portion of the meeting or work related to the declared interest and from the corresponding decision making process); or (iii) mandates total exclusion (i.e., you will not be able to participate in any part of the meeting or work).

All potentially significant interests will be disclosed to the other participants at the start of the activity and you will be asked if there have been any changes. A summary of all declarations and actions taken to manage any declared interests will be published in resulting reports and work products. Furthermore, if the objectivity of the work or meeting in which you are involved is subsequently questioned, the contents of your DOI form may be made available by the Secretariat to persons outside WHO if the Director-General considers such disclosure to be in the best interest of the Organization, after consulting with you. Completing this DOI form means that you agree to these conditions.

If you are unable or unwilling to disclose the details of an interest that may pose a real or perceived conflict, you must disclose that a conflict of interest may exist and the Secretariat may decide that you be totally recused from the meeting or work concerned, after consulting with you.

**Name:**
**Institution:**
**Email:**

**Date and title of meeting or work, including description of subject matter to be considered (if a number of substances or processes are to be evaluated, a list should be attached by the organizer of the activity):**

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

Please answer each of the questions below. If the answer to any of the questions is "yes", briefly describe the circumstances on the last page of the form.

The term "you" refers to yourself and your immediate family members (i.e., spouse (or partner with whom you have a similar close personal relationship) and your children). "Commercial entity" includes any commercial business, an industry association, research institution or other enterprise whose funding is significantly derived from commercial sources with an interest related to the subject of the meeting or work. "Organization" includes a governmental, international or non-profit organization. "Meeting" includes a series or cycle of meetings.
**EMPLOYMENT AND CONSULTING**

*Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work?*

1a Employment

[ ] Yes [ ] No

1b Consulting, including service as a technical or other advisor

[ ] Yes [ ] No

**RESEARCH SUPPORT**

*Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of the meeting or work?*

2a Research support, including grants, collaborations, sponsorships, and other funding

[ ] Yes [ ] No

2b Non-monetary support valued at more than US $1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.)

[ ] Yes [ ] No

Support (including honoraria) for being on a speakers bureau, giving speeches or training for a commercial entity or other organization with an interest related to the subject of the meeting or work?

**INVESTMENT INTERESTS**

*Do you have current investments (valued at more than US $5 000 overall) in a commercial entity with an interest related to the subject of the meeting or work? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.*

3a Stocks, bonds, stock options, other securities (e.g., short sales)

[ ] Yes [ ] No

3b Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company)

[ ] Yes [ ] No

**INTELLECTUAL PROPERTY**

*Do you have any intellectual property rights that might be enhanced or diminished by the outcome of the meeting or work?*

4a Patents, trademarks, or copyrights (including pending applications)

[ ] Yes [ ] No

4b Proprietary know-how in a substance, technology or process

[ ] Yes [ ] No

**PUBLIC STATEMENTS AND POSITIONS** (during the past 3 years)

5a As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of the meeting or work, for a commercial entity or other organization?

[ ] Yes [ ] No

5b Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work?

[ ] Yes [ ] No

**ADDITIONAL INFORMATION**

6a If not already disclosed above, have you worked for the competitor of a product that is the subject of the meeting or work, or will your participation in the meeting or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage?

[ ] Yes [ ] No

6b To your knowledge, would the outcome of the meeting or work benefit or adversely affect interests of others with whom you have substantial common personal, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)?

[ ] Yes [ ] No

6c Excluding WHO, has any person or entity paid or contributed towards your travel costs in connection with this WHO meeting or work?

[ ] Yes [ ] No
6d Have you received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this WHO meeting or work? □ Yes □ No

6e Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence? □ Yes □ No

7. **TOBACCO OR TOBACCO PRODUCTS** *(answer without regard to relevance to the subject of the meeting or work)*

   Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity? □ Yes □ No

**EXPLANATION OF "YES" RESPONSES:** If the answer to any of the above questions is "yes", check above and briefly describe the circumstances on this page. If you do not describe the nature of an interest or if you do not provide the amount or value involved where relevant, the conflict will be assumed to be significant.

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<th>Nos. 1 - 4: Type of interest, question number and category (e.g., Intellectual Property 4.a copyrights) and basic descriptive details.</th>
<th>Name of company, organization, or institution</th>
<th>Belongs to you, a family member, employer, research unit or other?</th>
<th>Amount of income or value of interest (if not disclosed, is assumed to be significant)</th>
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CONSENT TO DISCLOSURE. By completing and signing this form, you consent to the disclosure of any relevant conflicts to other meeting participants and in the resulting report or work product.

DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge.

Should there be any change to the above information, I will promptly notify the responsible staff of WHO and complete a new declaration of interests form that describes the changes. This includes any change that occurs before or during the meeting or work itself and through the period up to the publication of the final results or completion of the activity concerned.

Date: ________________    Signature________________________________