



**Expanded Programme on Immunization (EPI)  
Department of Immunization, Vaccines and Biologicals (IVB)  
Family, Women, Children and Adolescents (FWC)  
World Health Organization (WHO)**

**Request for Proposals**

**Waning Immunity and its potential impact on elimination**

**Deadline for application: 15 February 2018**

***Introduction***

In 2012, WHA endorsed the Global Vaccine Action Plan 4 with the objective to eliminate measles in four WHO regions by 2015 and in five regions by 2020. Countries in all six WHO regions have adopted goals for measles elimination by, or before, 2020. Measles elimination is defined as the absence of endemic measles virus transmission in a region or other defined geographical area for  $\geq 12$  months, in the presence of a well-performing surveillance system. So far, the Region of the Americas has been verified as having eliminated measles, and several countries in the Western Pacific, European and South East Asian WHO regions have been verified as having eliminated measles. As measles elimination needs to be sustained over many years, waning immunity to measles virus becomes a potential concern. Vaccine-derived immunity is less durable than immunity derived from infection with wild-type measles virus. The rate at which antibody titres and cellular immunity are observed to wane may be accelerated in elimination settings due to a lack of immunological boosting from circulating wild-type measles virus. However, since levels of antibody and cellular immunity are merely markers of protective immunity, the most important question is whether actual protection against measles infection also wanes.

While information from areas which have achieved and sustained measles elimination over many years suggests that waning immunity may not be a problem in the shorter term, a problem may emerge over a longer time period. We know that it took many decades to achieve smallpox and polio eradication. As there is no current appetite for a global measles eradication target, we also know that vaccine-derived measles immunity may need to be sustained for many decades into the future. The duration of vaccine-derived protection that will be needed to sustain measles elimination may be much longer than the duration we have had the chance to observe so far in any country.

In elimination settings, waning protection might affect entire cohorts of vaccinated individuals. Understanding the current status and future implications of waning measles immunity in elimination settings is essential for updating current assumptions, including the required level of vaccine coverage to sustain elimination, the number of vaccine doses required and the schedule for possible booster doses, the susceptibility status of those born before endemic transmission ended in sustained elimination settings, who are often

considered to have high levels of long-lasting immunity through past natural infection, and the potential for longer term re-establishment of endemic measles virus transmission after elimination.

To address the aforementioned, a combination of systematic reviews and modelling would be required. The research questions should be derived from the following policy questions:

### ***Policy Questions***

The set of policy questions that arise from the idea of waning immunity are necessarily broader than the focused research questions that follow further on. These policy questions include the following:

- I. Is there evidence for waning vaccine effectiveness and humoral and cell-mediated immunity in adults who were vaccinated as children and who reside in measles elimination settings?
- II. Is there evidence for waning vaccine effectiveness and humoral and cell-mediated immunity in adults with a history of infection with wild-type virus living in measles elimination settings?
- III. What is the likelihood that population immunity could be reduced to below the critical immunity threshold?

### ***Deliverables***

The following are the required deliverables for this project:

#### **a. Systematic Reviews:**

Based on the above policy questions, research questions should be developed and a systematic review conducted to address the research questions.

#### **b. Mathematical modelling:**

Apply a simple mathematical model to address the following questions: How long would it take a population that is achieving the WHO target of 95% immunity in children to accumulate sufficient susceptible individuals through waning immunity that the population as a whole falls below the critical immunity threshold for sustaining elimination?

#### **c. Research gaps and further work:**

Based on the results of the systematic review and modelling, identify research gaps and how might they be addressed.

#### **d. A report containing the following:**

1. Executive summary.
2. Background.
3. Research question(s) and/or study objectives.
4. Search strategy for sources of evidence, including information on the databases and resources used.
5. Selection criteria for quality of evidence (inclusion and exclusion criteria).

6. Data collection and analysis (critical assessment), including, if applicable, statistical pooling, estimation or other techniques and methods applied.
7. Main results and/or main estimates.
8. Authors' conclusions on results and data quality and critical appraisal of evidence.
9. Citations and access to extracted data in a MS access or comparable format.

The Report should also:

- Include interpretative commentary with respect to sources of error, bias and missing data in the reviewed data.
- Identify key limitations in the data. The Report may also make suggestions for future research that is needed.

A representative of the research team (PI and/or deputy) will be expected to attend WHO expert consultations, as required (maximum of two meeting).

### ***Timeline***

From 12 February to 15 May 2018 for the draft report to be completed, with presentation at the Strategic Advisory Group of Experts (SAGE) Measles and Rubella working group meeting in July 2018 and final report to be submitted by 30 September 2018.

### ***Proposals***

An electronic copy of the Proposals in English should be submitted (**no later than 15 February 2018**) to:

Dr Alya Dabbagh

Expanded Programme on Immunization

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### ***Format and Contents***

- A one page Executive Summary must be provided which describes the manner in which the applicant proposes to meet WHO's requirements, and clearly and concisely state the major elements of the proposal.
- A methods sections clearly describing the methodology to be used to carry out the required work, the research questions and the Population Intervention Comparison Outcome (PICO) strategy.
- The budget requirements for the work to be carried out.
- The applicant profile which describes the organizational and individual(s) capacity to carry out the work and includes experience in similar projects, staffing capacity to undertake the current project and possible conflict of interest.