REQUEST FOR PROPOSALS

Systematic review and meta-analysis of the population-level impact and herd effects following human papillomavirus immunization programmes

1. Introduction
The WHO Initiative for Vaccine Research (IVR)\(^1\) is interested in a systematic review and meta-analysis of the population-level impact and herd effects following human papillomavirus (HPV) immunization programmes. We seek proposals to perform the systematic review, data extraction, and, where applicable, the related statistical analyses.

2. Background
Although they have been licensed since the mid-2000s, HPV vaccines remain arguably underutilized. As of January 2016, only 65 countries (34% of all countries) had introduced HPV vaccine in their national immunization schedules. Challenges in the uptake of HPV vaccines vary among countries. Research plays an important role in the policy-making of HPV immunization programmes, for instance by garnering the evidence to introduce the HPV vaccine and by putting forward changes that ease operational challenges.

WHO’s Strategic Advisory Group of Experts on Immunization (SAGE) made in October 2008 the first global recommendations on HPV vaccines. Based on the evidence available at that time, high coverage in a primary target of girls aged 9–13 years was recommended as the priority of HPV immunization programmes. After reviewing new data from clinical trials with 2- and 3-dose HPV vaccine doses, SAGE recommended in April 2014 an extended 2-dose HPV immunization schedule for girls aged 9–14 years, who are not immunocompromised.

WHO is committed to reviewing evidence continuously so that global immunization recommendations remain up-to-date. An ad-hoc expert consultation held in December 2015 mapped out issues related to HPV immunization that are worth considering. One of the identified issues was national licences starting in December 2014 of a 9-valent HPV vaccine, which includes five additional high-risk HPV types compared to the previously marketed bivalent and quadrivalent HPV vaccines. The 9-valent vaccine was licensed in 39 countries as of mid-April 2016. Another issue is the inclusion of boys in HPV immunization programmes as an incremental strategy to a vaccination targeting only girls and young women. Male HPV immunization is routine in a few high-income countries (i.e., Australia, Austria, Italy, Switzerland, USA, and six Canadian Provinces).

The systematic review and meta-analysis of the population-level impact and herd effects following HPV immunization programmes will provide a base of evidence that is relevant to several policy questions related to HPV vaccines. Namely, this evidence base may inform deliberations on HPV immunization during future SAGE meetings.

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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/)
3. **Purpose**

To perform a systematic review and meta-analysis of the population-level impact and herd effects following HPV immunization programmes from published and unpublished studies in females and males.

4. **Objectives**

The specific objectives are:

1. To identify published and unpublished time-trend studies that analysed changes in HPV-related endpoints before and after HPV vaccine introduction;
2. To review systematically evidence on changes in prevalence/incidence in HPV infection, precancerous cervical lesions, and anogenital warts;
3. To extract prevalence/incidence data globally and stratified by vaccine type, vaccination coverage, number of vaccine doses, years since vaccine introduction, geographical areas, and sex; and
4. If methodologically warranted, to perform statistical analyses and critical appraisal of the extracted dataset.

Successful applicant teams will use replicable strategies for literature search and data extraction and analysis. The systematic review and meta-analysis should be conducted following the SAGE Guidance for development of evidence-based vaccine-related recommendations and in accordance with international standards for the analysis and reporting of systematic reviews (e.g. PRISMA, COCHRANE Handbook and MOOSE). This should include but need not be limited to the production of descriptive tables summarizing the information about the study design, risk of bias and results of all included studies, the quantification of the variation in prevalence/incidence according the characteristics of individuals and studies, and the use of the GRADE approach to assess the strength of the conclusions.

5. **Deliverables**

A protocol is due **within 3 weeks** of agreement signature.

An interim report that outlines performed activities, preliminary results and challenges is due **by 18 July 2016**.

A final report will be due **on 18 September 2016**. The final product will be a systematic review report including the following elements:

- executive summary including objectives and main findings;
- research questions(s) and study objectives;
- short description of the methodology;
- table of retrieved and retained studies organized by vaccine type, vaccination coverage, number of vaccine doses, years since vaccine introduction, geographical areas, and sex;
- tables of the prevalence/incidence data;
- data analysis (critical assessment), including statistical pooling or meta-analysis of data, if applicable;
- tables including GRADEing of the evidence for previously agreed critical outcomes; and
• main results and/or main conclusions of the statistical analysis in answering the initial research question(s).

A representative of the research team will be expected to attend at least two WHO expert consultations and present information about their work.

A comment period may begin following the submission of final reports to IVR. Within a reasonable amount of time following its submission, IVR may initiate a peer review of the final report and submit questions and comments. In that case, the research team is expected to provide a written response to IVR on how the comments were addressed.

Public release of the final report may occur after the review process is completed. While a draft manuscript is not a requirement or deliverable of this project, the research team is encouraged to publish the content of the final report in an appropriate peer-reviewed journal.

All rights in the work, including ownership of the original work and copyright thereof, shall be vested in WHO, which reserves the right:

• to revise the work,
• to use the work in a different way from that originally envisaged, or
• not to publish or use the work.

The data will be posted in a public website, as appropriate.

6. Proposal submission

The following information should be included within the submission (maximum of 5 pages):

• Project description with goals and objectives;
• General information about the planned research team, including roles and responsibilities on this project;
• Information on anticipated involvement of any partner organizations, if applicable;
• Project budget, included costs per task and, if appropriate, the applicable Programme Support Cost;
• Projected timeline that consider the deliverables;
• Anticipated challenges for this particular project regarding time, organization, and management and how the research team proposes to meet those challenges;
• Declaration of conflicts of interest for all named persons on the research team (with WHO disclosure form); and
• Contact information for your organization including the full name of the organization, address and, if applicable, a signed cover letter from an institutional official supporting the submission.

7. 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 (the principal investigator should have at least five years of experience in both systematic reviews and statistical analysis);
• Methodological rigor of their proposed approach, including feasibility of timelines;
• Plans for leveraging previous systematic reviews and meta-analyses specifically related to the research objectives;
• Proposed timelines and likelihood to meet deadlines;
• Proposed budget/overall value of the project; and
• Adequacy of mechanisms for addressing any intellectual and financial conflicts of interest.

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.

8. Submission of proposal

Proposals must be submitted by email to vicarian@who.int. The electronic submission must be received by 5 June 2016 and, should include “IVR – Systematic review and meta-analysis of population-level impact following HPV immunization” in the subject line.