RFP REF. NO: IVI-DGO/2023-0001

Request for Proposal (RFP)

SAVAC sentinel sites for *Streptococcus pyogenes* disease epidemiological surveillance, health economic studies, and clinical trials

September 2023

Strep A Vaccine Global Consortium (SAVAC)

Hosted at:

International Vaccine Institute
Seoul, Republic of Korea

Funded by:

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1. PURPOSE

Streptococcus pyogenes (group A *Streptococcus*, "Strep A") infections result in a vastly underestimated burden of acute and chronic disease globally. Towards the aim to accelerate the development of vaccines against *Streptococcus pyogenes* the Strep A Vaccine Global Consortium (SAVAC) will support four sites in low- and middle-income countries to conduct surveillance of Strep A diseases in community and hospital-based settings as part of the SAVAC 2.0 grant supported by the Leducq Foundation and Open Philanthropy. Surveillance will comprise epidemiological and health economic studies. In addition, two of the selected sites will be prepared for future vaccine trials, including but not limited to the establishment of Strep A pharmacovigilance platforms.

The objective of this Request for Proposal (RFP) is to identify and contract sites for 35 months (total time frame) which includes a 24-month surveillance period plus 7 months for study preparation and 4 months for data analysis.
The applications are sought in two stages:

Stage I: Request for Letter of Intent (LOI)
Stage II: Request for Full Proposal Full Proposal (RFP) (shortlisted candidates will be contacted)

Screening of LOIs and down-selection of candidate sites for feasibility assessment, potential on-site visits, and requests of full proposal will start on Sep 20 and continue in a rolling review until Sep 29 (last day to submit an LOI).

2. ORGANIZATION OVERVIEW

The Strep A Vaccine Global Consortium (SAVAC, https://savac.ivi.int/about) was formed in 2019 and convenes representatives from the health sector with the mission to ensure that safe, effective and affordable Strep A vaccines will be available and implemented to decrease the burden of Strep A disease in the most in need.

SAVAC is hosted at the International Vaccine Institute (IVI), which will be the contracting organization. IVI is a nonprofit International Organization established in 1997 as an initiative of the United Nations Development Program (UNDP). IVI's mission is to discover, develop and deliver safe, effective, and affordable vaccines for global public health. IVI is headquartered in Seoul and hosted by the Republic of Korea with 36 member countries and the WHO on its treaty.

3. BACKGROUND

Strep A was estimated before the COVID-19 pandemic to be the 5th most frequent cause of death due to an infectious disease, with an estimated 639,000 deaths annually (Hand et al., in Hunter's Tropical Medicine and Emerging Infectious Diseases, Elsevier, 2020). The spectrum of Strep A diseases is broad from superficial infections (pharyngitis and impetigo) to invasive disease, cellulitis, toxin-mediated disease (Scarlet fever), immune-mediated conditions (acute rheumatic fever [ARF] and acute post-streptococcal glomerulonephritis [APSGN]) and chronic conditions (rheumatic heart disease [RHD] and chronic kidney disease). The greatest burden is due to RHD and lies in low- and middle-income countries. Despite this overall high burden, there are a limited number of vaccines under development currently. Several knowledge gaps resulting in this discrepancy were identified in the SAVAC 1.0 project, which was funded by the Wellcome Trust. These include the lack of detailed knowledge of the disease burden for the various specific clinical endpoints and particularly in low-and-middle-income countries. There is also a lack of adherence to recently developed standardized procedures for surveillance, specimen collection, and laboratory diagnostics. In addition, the SAVAC 1.0 project highlighted that economic evaluations for Strep A infections were scarce and reported that it is essential to increase primary health economic data points, particularly in LMIC settings.

Thus, an objective of SAVAC 2.0 is to establish 4 sentinel sites to collect detailed epidemiologic and economic data for Strep A infections. The burden of mild to moderate disease (pharyngitis, impetigo) in the community will be assessed through prospective surveillance of households. This will provide data across all ages and allow assessment of transmission events. Severe cases of invasive Strep A infection and auto-immune disease and sequelae across all ages will be assessed in hospital-based studies. Hospitalized cases of invasive Strep A disease, skin and soft tissue infection (including cellulitis), ARF/RHD and APSGN will be included. These data will be crucial for the clinical development of future vaccines, in particular the assessment of efficacy against

clinical endpoints and the detection of potential safety signals (Asturias et al., 2023, Clin.Infect.Dis.)

The individual studies are expected to be led by the sites. However, the studies at the 4 sites will be conducted in unison under a master protocol with harmonized procedures.

At two of the sites, in addition to the epidemiological studies, there will be activities around embedded health economics research, focusing on the estimation of the economic burden and cost-of-illness of selected Strep A diseases. An additional antibiotic use survey may also be considered after assessing each site.

Furthermore, two of the sites will be prepared as clinical trial sites for future Strep A vaccine trials. This will include the establishment of a pharmacovigilance platform, particularly for Strep A diseases, in preparations for vaccine safety surveillance. In addition, various trainings will be provided as applicable, e.g. in Good Clinical Practice (GCP), lab assays and procedures, Quality systems, etc.

Study site review will include baseline review, study site/staff experience in research, epidemiology, cardiology/rheumatic heart disease, pediatric care, ethical review, clinical trial execution, vaccine safety monitoring. None of these are considered necessarily exclusionary.

4. RFP SCOPE

The scope of this RFP is to evaluate the capability of sites to carry out the epidemiological studies, both in the community and in a hospital. In addition, the RFP will assess the capability and interest to engage in health economic and cost of illness studies as well as in preparations for future clinical trials with Strep A vaccine candidates, which both will be performed at the subset of the selected sites.

The scope for the epidemiological surveillance at all four sites includes:

- ✓ Conduct epidemiological surveillance for Strep A among a minimum of 500 participants, in approximately 100 households, with focus on:
  - Pharyngitis
  - Impetigo and other skin infections (e.g., pyoderma and cellulitis)
- ✓ Conduct surveillance of hospitalized cases with Strep A disease, primarily focused on severe endpoints as listed below at secondary and tertiary level hospital facilities, dependent on local factors:
  - Cellulitis, including erysipelas
  - Acute rheumatic fever (ARF)

- Rheumatic heart disease (RHD)
- Acute poststreptococcal glomerulonephritis (APSGN)
- Invasive Strep A infections (various manifestations)

✓ Site establishment:
- Interact with Ethics Committee (EC), Institutional Review Board (IRB), national committees and/or agencies as required
- Adaptation of harmonized study protocols and master study protocol (provided by SAVAC) to site requirements

✓ Specimen collection and microbiological diagnostics

✓ Specimen collection (serum) for immunology assessments

✓ Access and delivery of standard of care

✓ Duration: Total contract time is 35 months: 7 months of preparation, 24 months of surveillance, 4 months for data analysis

Further details for the community-based and the hospital-based studies are provided in **Appendix A**.

The scope for the additional health economic studies and/or preparation for clinical trial at a subset of sites includes:

✓ Conduct cost-of-illness (COI) studies by implementing individual-level surveys in the community and health facility settings: accessing and reviewing hospital records/invoices for enrolled COI patients in the case of health facility settings (may include a survey on antibiotic use in the community-based study)

✓ Establishment of a pharmacovigilance system (or adapting and strengthening the existing system) for safety assessment of vaccine candidates

✓ Engage in general preparations for future clinical trials with Strep A vaccine candidates, or demonstrate existing experience, including in but not limited to:
- Good Clinical Practice
- protocol development
- site SOPs
- quality assurance activities
- safety surveillance methodology, including but not limited to echocardiographic examinations and analyses
- preparation of agreements
- submissions to IRBs and National Regulatory Agencies (NRAs)

Further details about the health economic study are provided in **Appendix B**.
Further details for the preparations for future clinical trials with Strep A vaccine candidates are provided in **Appendix C**.

5. APPLICATION PROCESS

5.1. Eligibility Criteria

- The call is open to academic institutions, hospitals, non-profit research organizations, government research organizations, and international organizations
- Applicants must be a legal entity
- Sites must be situated in low- or middle-income countries
- The applicant should have experience with epidemiological surveillance and a demonstrated track record
- The applicant must have capacity to diagnose Strep A from clinical specimens (in house or by arrangement with a local/regional lab)
- Applicants must be able to conduct studies in a hospital (preferentially secondary or tertiary) as well as in a community setting

5.2. Application Timeline

The review of LOIs will be based on a rolling review.
For a first expression of interest an email may be sent to IVI (see 5.4).

Call for LOI submission opens	Sep 11 2023
Deadline for LOI submission	Oct 18, 2023
Screening of LOIs will start	Sep 20, 2023, 17:00 Korea Standard Time (KST)
Notification of shortlisted sites	Starting Oct 13 , 2023
Invitation and deadline to submit full proposal	Will be communicated through email to shortlisted applicants after screening of LOIs
Site feasibility visits	November to December 2023
Notification of decision to applicants*	End of January 2024

*All applicants will be notified of the award status after the evaluation process.

5.3. Requirements for the LOI

LOIs should follow the following guidelines:
- include the information requested in **Appendix D**
- any claims made in the answers should be supported by evidence
- be clearly readable documents written in English
- be no longer than 2 pages
- include a high-level budget (in USD)

5.4. Instructions for submission

Submit proposals in PDF file to: **International Vaccine Institute**

Jae In Lee. and Christiane Gerke
jaein.lee@ivi.int Christiane.Gerke@ivi.int
Use Subject title "LOI - SAVAC Group A Strep sentinel site".

If you have questions and or for an initial expression of interest, please contact:

Christiane Gerke (Christiane.Gerke@ivi.int) with cc. to: Jae In Lee (jaein.lee@ivi.int) and: Somyoung Cho (Somyoung.Cho@ivi.int)

6. EVALUATION OF CANDIDATE SITES

SAVAC will organize a review committee composed of experts in the field. The review committee will evaluate the applicant sites based on the full proposals and the outcomes of the feasibility visits, following the tentative criteria below with consideration to country context and capacity building.

1. **Study-enabling local capacity:**
   - Demonstratable significant burden of Strep A diseases
   - Existing research capacity and experience of researchers in surveillance studies
   - Demographic estimates for the proposed site's catchment population
   - Capacity to treat/manage cases detected through surveillance

2. **Institution**
   - Experience in communicable diseases surveillance
   - Existing capacity to collect outcomes of interest including severe outcomes
   - Established clinical guidelines for diagnosis and management of any or all Strep A diseases
   - Established guidelines or readiness to set up guidelines for routine blood culture of febrile cases
   - Data management capacity – collection and storage
   - Computer-based hospital patient data capture and invoice system
   - Availability of reliable and secure data room, computers, and internet connection, and of skills and knowledge required for data management

3. **Lab infrastructure capacity**
   - Existing laboratory to perform Strep A diagnostics and other tests
   - Experience with antibiotic susceptibility testing (AST)

4. **Regulatory/governance capacity**
   - Established typical duration of approval process (IRB, Ethics committee (EC), governance, other relevant procedures as applicable)
   - Evidence of national/local government, health facility, and/or community support
   - Ability to procure required reagents and materials locally or internationally

- Permission, willingness, and capacity to provide non-identifiable samples to other countries for future studies

5. **For sites also interested in future clinical trials:**
   - Interest in facilitating Strep A vaccine development
   - Experience with Phase I-III clinical trials
   - Pharmacovigilance experience and potentially existing platform
   - Willingness to work with manufacturers across regions with the aim to ensure equitable access to vaccines tested at the site
   - Established regulatory ecosystem for vaccine and vaccine trial approval
   - National interest in deployment of new vaccines, previous evidence of early adoption of new vaccines

7. APPENDIX A – Brief study outlines – epidemiological surveillance

The studies outlined below will conducted by each of the four sites.

7.1. Community-based surveillance study

Brief Title	Community-based surveillance for GAS
Study type	Observational

Study Design	Prospective observational study:
	- 500 participants in approximately 100 households with assumed 5 individuals per household on average (Rational for the participant number: a study with 500 participants would allow +/-4% precision around an estimate of 10% incidence of Strep A pharyngitis or skin infection, considering 24 months of surveillance and a design effect of 2.)
	- All ages in household, but at least two members must under 14 years of age
	- Active surveillance for clinical disease endpoints of:
	  ○ Pharyngitis
	  ○ Impetigo
	based on protocols developed during SAVAC 1.0 as described in ref 1, 2
	- Specimen collection (throat and skin swabs) and microbiologic testing: at study start, then every 1-2 weeks (visits by nurses, self-swabbing might be possible in some areas), and when cases are self-reported
	- Specimen collection g (serum) for serologic studies: at study start, then every 2-3 month or when cases are reported (might be a sub-cohort)

Duration	Surveillance period: 24 months Study preparations: 7 months Study close-out and analysis after completion of surveillance: 4 months Total granting period: 35 months
Primary Objectives	1. Determine the incidence of Strep A pharyngitis 2. Determine the incidence of Strep A skin infection (impetigo) 3. Determine the prevalence of Strep A pharyngeal carriage 4. Describe transmission characteristics of Strep A throat and skin infection 5. Collect specimens for microbiologic (molecular diversity of Strep A) and immunologic (immune response) research.
Secondary Objectives	1. Determine the frequency of antibiotic use and antibiotic class, if applicable
Study population	Households in the community; household members of all ages with at least two members under 14 years of age
Number of subjects	500 participants in approximately 100 households (continuous participation for the 24-months surveillance period) with assumed 5 individuals per household (on average) Must be enrolled in a time frame that allows completing 24 months surveillance within the granting period as well as data analysis
Case definitions	Refer to standardized protocols in references 1 and 2, to be adapted to site-specific settings
Inclusion criteria	1. Household has at least two children under 14 years of age 2. Usual resident of the household 3. Signed consent 4. Reasonably able to participant for the duration of the surveillance period

Exclusion criteria	1. Have a condition that restricts or be unwilling to provide the collection of necessary specimens
Biospecimen	1. Specimen collection for microbiology: throat swabs and skin swabs 2. Specimen collection for immunology: serum
Intervention	No intervention for pharyngitis and impetigo outside of any treatments given routinely. Standard care for identified severe cases
Comments	- SAVAC team will provide master study protocol - SAVAC epidemiological team will support the sites to implement harmonized surveillance methodologies and case definitions established in SAVAC 1.0 support laboratory development and to implement harmonized assays - SAVAC team will provide methods for data collection, including case report forms, a validated electronic data capture system (EDC), unified database, and data management training including system manual and electronic case report form completion guidelines. - Collected data will need to be kept in the validated EDC system. The high-quality of the data will need to be ensured by resolving data queries raised in the EDC system. - SAVAC data management team - For site who participate in the health economic study, the study population will be the same population as for the health economic study (see **Appendix B**)

7.2. Hospital-based surveillance study

Brief Title	Hospital-based surveillance for invasive and other severe Strep A diseases
Study type	Observational
Study Design	Observational study - Hospitalized cases of Strep A diseases - Microbiology sampling: Upon admission and before administration of antibiotics
Duration	Same as described in Appendix A, 7.1 community-based surveillance study
Primary Objectives	1. Determine the incidence of invasive Strep A disease 2. Determine the incidence of Strep A skin and soft tissue infection requiring hospitalization 3. Determine the incidence of ARF, RHD and PSGN requiring hospitalization 4. Collect specimens for microbiologic (molecular diversity of Strep A) and immunologic (immune response) research. 5. Determine case-fatality rates Surveillance procedure will follow the methodology developed in SAVAC 1.0 (ref 3-7) adapted to the sites
Secondary Objectives	1. Collect information of antibiotic use if applicable 2. Determine frequency of AST among Strep A isolates recovered Recor 3. Record pregnancy outcome for Strep A-infected pregnant women hospitalized for complications
Study population	Hospitalized individuals with invasive Strep A disease, skin and soft tissue

	infection (including cellulitis), ARF/RHD and PSGN
Number of subjects	All cases during the 2 years
Inclusion criteria	1. Patients living in the catchment area (including documentation where the patients normally live) 2. Strep A confirmation in case of acute disease, adherence to standardized diagnosis protocol for chronic disease, e.g. RHD
Exclusion criteria	Does not consent to collection of specimens/diagnostic tests?
Biospecimen	Collection of specimens for microbiology: throat swabs, sterilely collected specimens based on disease (e.g., blood, joint fluid, etc.)
Intervention	Standard care for cases. No additional intervention as part of the study.
Comments	- SAVAC team will provide master study protocol - SAVAC epidemiological team will support the sites to implement harmonized surveillance methodologies and case definitions established in SAVAC 1.0 support laboratory development and to implement harmonized assays - SAVAC team will provide methods for data collection, including case report forms, a validated electronic data capture system (EDC), unified database, and data management training including system manual and electronic case report form completion guidelines. - Collected data will need to be kept in the validated EDC system. The high-quality of the data will need to be ensured by resolving data queries raised in the EDC system. - SAVAC data management team - For site who participate in the health economic study, the study population will be the same population as for the health economic study (see **Appendix B**)

References:

Standardized surveillance protocols for 7 Strep A Disease Endpoints are available at: Volume 9 Issue Supplement_1 | Open Forum Infectious Diseases | Oxford Academic (oup.com)

1. Pharyngitis - https://doi.org/10.1093/ofid/ofac251
2. Impetigo - https://doi.org/10.1093/ofid/ofac249
3. Invasive Strep A disease - https://doi.org/10.1093/ofid/ofac281
4. ARF - https://doi.org/10.1093/ofid/ofac252
5. RHD - https://doi.org/10.1093/ofid/ofac250
6. APSGN - https://doi.org/10.1093/ofid/ofac346
7. Cellulitis - https://doi.org/10.1093/ofid/ofac267

8. APPENDIX B – Brief Study outline – health economic and cost of illness study

At two of sites, health economic and cost-of-illness studies will be conducted.
These will be added to the community- and hospital-based studies described above in Appendix A.

Brief Title	Health economics and cost of illness study in community and hospital settings
Study type	Economic burden estimation for selected GAS infections
Study Design	- Linked to the community- and hospital-based surveillance studies outlined above in Appendix A - Implementation of individual-level surveys for the cost-of-illness studies in the community setting - Implementation of patient-level surveys for the cost-of-illness studies and access to hospital records/invoices in the hospital setting
Duration	Same as described in Appendix A, 7.1 community-based surveillance study
Primary Objectives	Estimate the cost-of-illness (COI) of selected GAS diseases in community-and hospital-based settings: 1. Hospital-based setting - Private cost estimation (out-of-pocket) and public cost estimation 2. Community-based setting - Mainly private cost estimation
Secondary Objectives	Estimate the frequency of antibiotic use in the community-based setting
Study population	COI patients will be enrolled through the surveillance system.
Number of subjects	All subjects agreed to participate in the COI study (more details on sample size will be provided after finalizing the set of GAS infections for the COI study)
Case definitions	Same as the surveillance criteria
Inclusion criteria	1. Eligible for inclusion in the surveillance study AND 2. Lab confirmation or clinical suspicion AND 3. Willing and able to consent for the COI study
Comments	- SAVAC will design/implement the overall HE/COI study, provide training to the HE focal points (1-2 per site) prior to the study implementation, follow up on data collection and carry out analyses. - HE/COI interviews will be conducted by local staff (there will be follow-up (multiple) interviews per patient). - Hospital record (billing/invoice) system needs to be accessible for the COI enrolled patients. - Interviewers (or the person supervising the interviewers) will be the focal points to the SAVAC team.

9. APPENDIX C – Preparations for clinical trials

Two of the sites will be further developed to conduct clinical trials in the future with Strep A vaccine candidates. Such trials may comprise Phase I to Phase III, dependent on site capacity.

The development of Strep A vaccine clinical trial site capacity may build on already existing capacity to conduct clinical trials with investigational products and/or be part of capacity building at interested sites. SAVAC will work with the sites and preform on-site assessments to identifying potential gaps and discuss with potential investigators and key personnel. Where applicable, SAVAC will provide hands-on training.

The development is envisioned in two parts.

1. Establishment of a pharmacovigilance system for safety assessment of vaccine candidates. This will include general procedures used for any vaccine candidate and specific methods for safety assessment of Strep A vaccines. A particular focus will be on echocardiography examinations (including with hand-held echocardiograms) and analysis as well as assays to detect potentially induced cross-reactive antibodies. A working group within SAVAC is developing recommendations for safety follow up of Strep A vaccine candidates and these outcomes will be implemented at the clinical trial sites.

2. General development and/or training for clinical trials with investigational products, with specific focus on trials with Strep A vaccine candidates, or demonstrate existing experience and logistics in:
    - Good Clinical Practice
    - project management
    - operational aspects including study overview, visit procedures, safety reporting, Investigational Product management, completing study log & forms, operation manuals
    - protocol development
    - site SOPs
    - lab sample management and logistics
    - quality assurance activities
    - safety surveillance methodology
    - routine safety biological testing (urine, hematology, liver and kidney functions)
    - data management
    - reliable power supply, internet provider, Microsoft office capabilities
    - storage space, refrigerators, and freezers
    - access to international transportation
    - receipt and storage of reagents and vaccines
    - community engagement
    - preparation of agreements
    - budget preparation and accounting procedures
    - approval process understanding and submissions to IRBs and NRAs

These activities will be carried out in parallel to the surveillance study.

10. APPENDIX D – Questions for the LOI

LOI Short Title: SAVAC - Group A Strep sentinel site

1. Describe your interest in the studies and applicable experience of the PI and key personnel.

2. Describe the Strep A prevalence for each Strep A disease tracked at your site, as known today.

3. Describe your organization and where the surveillance will take place and provide key characteristics of the site

4. Describe the hospital and facilities. Also include:
   - The estimated catchment population
   - How many patients you would expect to enroll in the hospital-based study based on experience in previous years (if applicable)
   - If you routinely do blood cultures in case of febrile infections
   - If you regularly conduct echocardiogram analyses of potential ARF and RHD cases
   - If you have a computer-based data entry and invoicing system at the hospital

5. Describe the community in which you would enroll particpants. Also include:
   - How much time you think you will need to enroll 500 participants, approximately 100 households
   - If you have knowledge about the Strep A pharyngitis and impetigo occurrence in the community

6. Describe the approval process for the proposed studies (ethics committee, national committees if appliable, etc) and typical duration of the process from submission to approval

7. If you are interested in the preparations for future clinical trials for GAS vaccines please include:
   - If you already have experience with clinical trials. If yes, please elaborate.
   - If you already have a pharmacovigilance platform in place. If yes, please describe.
   - If you have already worked with vaccine developers from different regions or if you are willing to do so with the aim to achieve equitable access of vaccine candidates that might be tested at you site. If yes, please elaborate.

8. Provide a high level budget estimate