REQUEST FOR LETTER OF INTEREST

Real-world Studies on the Effectiveness of China-made COVID-19 Vaccines

COVID-19 Vaccines Evaluation Program (COVEP)

I. Introduction

- **Background**

The COVID-19 pandemic remains a global health crisis and major challenge for all countries. Although public health measures have been implemented worldwide, the virus continues to spread, threatening people's health and well-being. Many healthcare systems and the global economy are in distress. Immunization with safe and effective COVID-19 vaccines, in conjunction with other public health measures, holds promise to reduce further loss of life and economic disruption and help return to normal life.

- **China-made COVID-19 vaccines and domestic use**

To date, seven China-made vaccines have been approved by China's vaccine regulator, the National Medical Products Authority (NMPA), and are being used in and outside of China[1]. Four vaccines are approved for conditional use and three are approved for emergency use (Supplement Table 1). The World Health Organization (WHO) has approved two of the China-produced vaccines for Emergency Use Listing, and the WHO Strategic Advisory Group of Experts on immunization (SAGE) has recommended these two inactivated COVID-19 vaccines for global use (Sinopharm and Sinovac COVID-19 vaccines)[2,3]. Two additional China-made vaccines - CanSino's adenovirus-vectored COVID-19 vaccine and Zhifei Longcom's recombinant protein COVID-19 vaccine - are under review by the WHO Emergency Use Listing (EUL)/Prequalification (PQ) program[4].

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[1] https://www.globaltimes.cn/page/202108/1231387.shtml

[2] https://www.who.int/news/item/01-06-2021-who-validates-sinovac-covid-19-vaccine-for-emergency-use-and-issues-interim-policy-recommendations

[3] https://www.who.int/news-room/feature-stories/detail/the-sinopharm-covid-19-vaccine-what-you-need-to-know

[4] https://www.who.int/teams/regulation-prequalification/eul/covid-19

In more than a dozen countries, interim data from Phase III clinical trials have demonstrated the immunogenicity, safety, and efficacy of four of the seven China-made COVID-19 vaccines. These Phase III clinical trials were all conducted overseas due to a very low rate local transmission of SARS-CoV-2 in China that occurs only in small and unpredictable importation outbreaks. Efficacies of these vaccines for reducing overall, mild, severe, and fatal cases among adults have met the WHO COVID-19 vaccines Target Product Profile efficacy targets[5], and the evaluation guidelines by China NMPA[6]. WHO/SAGE and WHO/EUL noted that some populations, including the elderly and people with comorbidities, were not sufficiently represented in the Phase III clinical trials to produce efficacy estimates. Thus, real-world, observational evidence is needed to understand the full range of performance of the China-made COVID-19 vaccines[7].

China has been using the China-made COVID-19 vaccines since July 2020, initially under EUL by NMPA, and since December 2021, under NMPA conditional approval and EUL[8]. The strategy for vaccination in China started with protection of frontline workers at occupational risk of infection, followed by vaccination of working-age adults, elderly adults and those with comorbidities, and adolescents. As of the end of August 2021, more than two billion doses of COVID-19 vaccines have been administered in China[9]; the vast majority of these doses have been inactivated vaccines. The safety of China-made COVID-19 vaccines is being monitored carefully through a nationwide real-time AEFI surveillance system jointly managed by the Chinese Center for Disease Control and Prevention (China CDC) and NMPA. AEFI surveillance data have provided confidence about the safety of China-made vaccines, with strong evidence showing very low reactogenicity and no serious safety signal after administration of two billion doses[10].

- **Global use and rational of Overseas VE studies**

China has provided more than 700 million doses of COVID-19 vaccines globally. President Xi Jinping has pledged to provide two billion doses of COVID-19 vaccines

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[5] https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines
[6] http://www.gov.cn/xinwen/2020-08/15/content_5535069.htm
[7] Mallapaty, S. (2021). China's COVID vaccines are going global-but questions remain. Nature, 593(7858), 178-179.(https://www.nature.com/articles/d41586-021-01146-0)
[8] http://weekly.chinacdc.cn/en/article/doi/10.46234/ccdcw2021.083
[9] http://www.nhc.gov.cn/jkj/s7915/202109/3dfd6315f9234a9da1622d2cd68df98f.shtml
[10] https://www.cdr-adr.org.cn/drug_1/aqjs_1/drug_aqjs_sjbg/202105/t20210528_48651.html

to the world to promote equity and access of COVID-19 vaccines as a public good[11]. With the increasing domestic and global use of China-made vaccines, conducting real-world vaccine effectiveness (VE) studies of China-made COVID-19 vaccines is critically important. VE studies provide essential evidence for assessing vaccine performance, which in turn supports development and refinement of COVID-19 immunization strategies, updating COVID-19 prevention and control strategies, and full regulatory approval following emergency use listing (EUL) or conditional approval. VE studies can offer evidence to support global use of vaccines during and after EUL, and can help determine the potential impact of vaccines on the global COVID-19 pandemic. However, due to the very small amount of domestic transmission of SARS-CoV-2 within China, conducting a sufficient number of appropriately-sized COVID-19 VE studies to address some of the important vaccine effectiveness questions is not possible in China. Although some real-world studies can be conducted during importation outbreaks, the outbreaks in China are small due to large scale responses that stop the outbreaks, leaving several vaccine effectiveness questions unable to be addressed in a timely manner, or even addressed at all.

- **Introduction of the research program**

To address the need for evidence from overseas studies, China CDC, the leading national public health technical agency in China, is establishing a research program that will sponsor VE studies in countries using China-made COVID-19 vaccines. Appropriate settings are ones in which a significant proportion of a target population is vaccinated with a China-made vaccine, the epidemiological situation is conducive to conducting real-world VE studies, a local institution is available and has sufficient research capacity, and a local Principal Investigator (PI) is interested and motivated to conduct VE studies. Profiles of the China-made COVID-19 vaccines current in use globally are in the supplementary table.

China CDC has overall responsibility of this research program, which is called COVID-19 Vaccines Overseas Evaluation Program (COVEP). Two working arrangements are supported in COVEP: investigator-initiated grants and cooperative agreements. China CDC will provide funding to institutions for investigator-initiated grants and will provide both funding and technical support for cooperative

[11] http://en.qstheory.cn/2021-08/06/c_649087.htm

agreements. China CDC will seek interested PIs and their institutions.

II. Objectives and scope of this Request for Letters of Interest

The objective of this Request for Letters of Interest (RFLoI) from the China CDC COVEP office is to identify interested PIs and their institutions that have adequate resources and sufficient research experience and capacity, are located in a SARS-CoV-2 virus epidemic settings that use a considerable number of China-made COVID-19 vaccine to support real-world VE studies of one or more China-made vaccine. We will support studies of China-made vaccines that have WHO EUL, are seeking WHO EUL, or have sufficient bilateral use - currently, inactivated, adenovirus-5-vectored, and recombinant subunit COVID-19 vaccines.

We encourage research proposals in four priority areas: vaccine effectiveness, duration of protection and booster dose effectiveness, vaccine impact on the COVID-19 pandemic, and severity of breakthrough infections for safety monitoring.

1. Real-world evidence on vaccine effectiveness (VE)

We are seeking the following real-world evaluations of VE with China-made vaccines to augment evidence from Phase III clinical trials.

1.1 VE among the general population and the elderly, adolescents, and people with chronic conditions or comorbidities.

1.2 VE for different clinical outcomes (infection, symptoms/sign of infection, severe illness and death).

1.3 VE for different primary vaccination schedules and numbers of doses.

1.4 VE against variants of concern (VOCs).

1.5 VE of heterologous primary schedules.

2. Vaccine protection duration and effectiveness of booster doses

The durability and persistence of vaccine protection helps determine the necessity and timing of booster doses and helps to adjust strategies to control or possibly eliminate infectious diseases. Research is needed that address the following topics:

2.1 Duration of protection over time by severity of illness.

2.2 Factors that influence duration of protection (e.g., vaccine type, schedule, dose, age, VOC).

2.3 Necessity of booster doses and optimal timing of booster doses if necessary.

2.4 Effective schedules for heterologous boosting.

2.5 Duration of protection from booster-dose schedules.

2.6 Correlation of vaccine-induced protection with antibody persistence.

3. Vaccine impact on the COVID-19 pandemic

COVID-19 vaccination may reduce the spread of the virus through direct and indirect protection of the population, thereby affecting population transmission dynamics. The impact of vaccination on community transmission and the pandemic at a population level needs further investigation. We seek studies on the following.

3.1 The impact of vaccination schedules, population immunization strategies, and vaccination coverage on the effective reproduction number R_t, virus transmissibility ability, and velocity of spread.

3.2 The impact of vaccination program changes on the spectrum of clinical illness and on COVID-19 incidence, severity, and stress to the healthcare systems.

4. Severity of breakthrough infections for safety monitoring in high force of infection settings

A theoretical but as of yet unseen risk of COVID-19 vaccines is risk of exacerbating COVID-19 severity via antibody-dependent enhancement (ADE) and the occurrence of vaccine-associated enhanced disease (VAED). There is no biomarker for enhanced disease, and it is not currently possible to distinguish a severe breakthrough case from enhanced disease. Whether vaccines have ADE/VAED related risk needs to be further assessed by comparing breakthrough infections with unvaccinated cases in observational studies.

4.1 Assess severity of breakthrough infections for safety monitoring.

Several of the research questions are inter-related. As the pandemic situation changes over time, new research questions are likely to emerge. One study design may be able answer multiple questions and any one question may be answerable through different methods. COVEP, therefore, is willing to support a variety of approaches to one or more research topics, including supporting a PI/institution combination that will address a series of relevant questions over time.

III. Applicant eligibility criteria

- The applicant organization should be in a country that is using China-made COVID-19 vaccines or has plan to initiate use of China-made vaccines before the end of 2021.
- The funding opportunity is open to the following types of organizations:
    - National or subnational health department or public health technical agencies.
    - Academic institutions, such as universities and research agencies.
    - International agencies with the capacity to conduct studies in selected countries.
- The PI should have experience on conducting vaccine trials and/or observational studies.
- The proposed study should address at least one of the priority research questions described above, and it may address additional, investigator-proposed, related topics.
- The estimated budget should range from 100,000 to 1,000,000 USD for each project according to the research questions, study designs, and whether a series of studies will be conducted over time. Anticipated budget requests exceeding the upper limit should be discussed with COVEP prior to application.
- The PI and institution will share study reports and non-individually-identifiable data with COVEP (China CDC).

IV. Applicant guidelines and the review process

There will be two rounds of selection for the grant application: a Letter of Interest followed by a full proposal if the LOI is selected.

Letter of Interest

Letters of Interest will be evaluated on the feasibility and robustness of the research design and implementation plan, and the readiness and capacity of the research team and affiliated institutions. The following should be descripted in a Letter of Interest:

- Vaccine(s) to be evaluated
  - Which China-made vaccine(s) will be evaluated;
  - What other vaccines, if any, will be evaluated?
- Study question(s)
  - Which of the RFLoI questions or topics will be addressed;
  - If a study question is not listed in this RFLoI, briefly describe the question and its importance.
- Basic study design
  - Target population
  - Research methods, including but not limited to
    - Prospective/historical prospective cohort study
    - Case-control, test-negative design (TND) study
    - Screening method study
    - Quasi-experimental study
    - Other design.
- Feasibility
  - China-made vaccine doses administered and approximate coverage, or planned amounts of China-made vaccine in the research area.
  - Ability to access data relevant to the study, for example, disease surveillance system data and vaccination registry or immunization information management system data.
  - Access to relevant vaccine safety surveillance data (AEFI surveillance system) for the study.
  - Description of COVID-19 epidemiology including the epidemic trajectory.
  - Availability of relevant laboratory data, including rapid tests, PCR, and genetic sequencing.
- Estimated budget
  - The estimated budget should range from 100,000 to 1,000,000 USD for each project according to the research questions and study design.
  - Need for a higher funding level should be discussed prior to submission of

the Letter.

- Duration of project
  - Project duration is suggested for 6-12 months, generally not more than 1.5 years.
  - Result should be available by the end of the project period and at the end of each individual study for institutions conducting a series of related studies.
- Collaboration approach with China CDC
  - Investigator-initiated grant. COVEP (China CDC) will support funding, and use of technical assistance from China CDC is available but optional.
  - Cooperative agreement. COVEP (China CDC) will provide funding and the applicant is responsible for developing the study protocol and implementing the protocol, but China CDC will be involved in study design, data analysis, outcomes reporting, and publication.
- Research capacity and resources
  - Vaccine related research experience of the applicant's team. A Curriculum Vitae (4 page maximum) of the Principal Investigator and key team members demonstrating qualifications and experience of the research team.
  - Presence of an Institute Review Board (IRB) for ethical approval by the PI's institution.
  - If applicable, include letters of support from collaborating governmental or non-governmental institutions.
- Applicant information
  - Name and title of applicant
  - Type of organization (e.g., governmental, non-profit, university, etc.).
  - Address and contact information
  - Signature of authorized representative of the applicant and institution.

VI. Submission of Letters of Interest

There are two deadlines for consideration of letters of interest (LOIs): 10 Novenber 2021 and 31 December 2021. LOIs will be reviewed in two independent rounds, and after each round, some LOIs will be requested for full proposal submission. Earlier submission is encouraged. Letters of Interest should be addressed to China CDC COVEP office (E-mail: xgproject@chinacdc.cn) with subject field indicating COVEP

application + name of applicant. The application should be in pdf format. The LOI template is in the appendix and can be downloaded at (https://www.chinacdc.cn/en/covid19/covep).

For selected LOIs, applicants will be requested to submit a full proposal for funding including relevant details for a grant or a cooperative agreement.

Technical and administrative questions about this Call should be directed to xgproject@chinacdc.cn

Appendix:

Letter of Interest

COVID-19 Vaccines Evaluation Program (COVEP)

Name of Applicant		**Organization**	
Email		**Tel**	
Country and Address			
Vaccine(s)	(Specify China-made vaccines; other sourced vaccines may also be evaluated)		
Study Question	(Briefly describe the study question)		
Population	(Describe the study population and the vaccine target population)		
Study Design	(Describe the study design and relevant methods)		
Feasibility	(Briefly describe the vaccination strategy, and any study-relevant immunization systems, disease surveillance systems, and AEFI surveillance systems; the COVID-19 epidemic situation; and access to necessary data.)		
Estimated Budget	(Overall estimated budget, separated into major line items, such as salaries, equipment, sub-contracts)		
Timeline	(Suggested for 6-12 months, maximum 18 months)		
Collaboration approach	(Investigator-initiated grant or cooperative agreement)		
Research capacity	(Briefly describe the applicant's team experience on vaccine related research, support from the institution, and the potential local collaborators. CV and supporting letters can be attached to the LOI.)		

Applicant Signature	Name: Title:	Date:
Organization Authorized Representative Signature	Name: Title:	Date:

*The length should be within 4 pages.

Supplement Table

Types of approved China-made COVID-19 vaccines

Platform	Name of Vaccine	Manufacturer	Recommended Schedule	Licensure in China	WHO EUL	Export
Whole virus inactivated vaccines	COVILO 众爱可维	Beijing Institute of Biological Products Co., Ltd, Sinopharm	2 doses >3 weeks interval	Conditionally approved 2020/12/30	**Yes**	**Yes**
	CoronaVac 克尔来福	Sinovac Biotech Ltd.	2 doses >3 weeks interval	Conditionally approved 2021/2/25	**Yes**	**Yes**
	COVILO 众康维乐	Wuhan Institute of Biological Products Co., Ltd, Sinopharm	2 doses >3 weeks interval	Conditionally approved 2021/2/5		
	KCONVAC 可维克	Shenzhen Kangtai, Biological Products Co., Ltd.,	2 doses >4weeks interval	Emergency use		
	科维福™	Institute of medical biology, Chinese academy of medical sciences	2 doses >3 weeks interval	Emergency use		
Adenovirus vectored vaccine	Convidecia 克威莎	CanSino Biologics Inc.	1 dose	Conditionally approved 2021/2/25		**Yes**
Recombinant protein vaccine	Zifivax™ 智克威得	Zhifei Longcom Biopharma & CAS recombinant protein vaccine	3 doses >4 weeks interval	Emergency use		**Yes**