HUMAN VACCINES PROJECT

COVID Vaccine Initiative

Ensuring vaccines are developed for those most vulnerable

Executive Summary: *Today, the world is facing the COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing over 6 million cases and 350,000 deaths so far, while ravaging many economies. Development of a COVID-19 vaccine has been placed on global emergency footing, but faces daunting challenges, including that vaccines are less effective precisely among groups most vulnerable to COVID-19, aging populations and those living in low and middle-income countries (LMICs), where deployment of vaccines has also historically been difficult. Thus, it is likely that COVID-19 vaccines currently in development will not be as effective in these key demographics, posing challenges towards ending the pandemic. The Human Vaccines Project, a global human immunology-centered clinical research consortium, with significant expertise in accessing aging populations and comprehensively evaluating vaccines, has established the COVID Vaccine Initiative (CVI) to address these challenges, with the mission to ensure that COVID-19 vaccines are developed for and accessible by those most vulnerable. The CVI leverages partnerships with major COVID-19 vaccine developers; collaboration with the Harvard T.H. Chan School of Public Health focused on aging populations; capabilities for research in LMICs via partnerships with FHI 360 with clinical capacity in more than 50 countries and South Africa's Aurum Institute with clinical research experience across the region; and the Center for Infectious Disease Research and Policy (CIDRAP; U. Minnesota) with a track record for translating science to policy. CVI will undertake scientific, advocacy and policy programs which collectively will define the course of COVID-19 disease and evaluate COVID-19 vaccines in these vulnerable populations, including demonstration projects with licensed vaccines, to facilitate global licensure and deployment. CVI not only will accelerate development of vaccines essential for ending the COVID-19 pandemic, but will provide foundational knowledge and capacity-building at LMIC study sites to combat future pandemics, and to facilitate prevention of major diseases in aging populations and those living in the developing world.*

A century ago, the 1918 influenza pandemic killed over 50 million people, more than all who died in World War I. Today, the world is facing its greatest pandemic threat since that time as SARS-CoV-2, the virus causing COVID-19 disease, which has spanned the globe in less than 6 months causing over 6 million cases, and over 350,000 deaths. More easily transmissible and deadlier than influenza, disease modelers now estimate that billions may become infected and millions may die as the virus emerges in sequential waves, with the highest rates of morbidity and mortality occurring in older adults with co-morbidities and those living in low- and middle-income countries (LMICs). For a range of other diseases including influenza and pneumonia caused by respiratory syncytial virus, vaccine effectiveness is reduced in these populations, due to weakened, aging or sub-optimal immune systems, and it is not clear that the COVID-19 vaccines currently in development will effectively protect these key demographics, posing challenges towards ending the global pandemic..

In response, the **Human Vaccines Project (HVP)** a nonprofit consortium focused on deciphering the rules for generating effective immunity in vulnerable populations, has launched the **COVID Vaccine Initiative (CVI)** as a targeted initiative to ensure the development of safe, effective, accessible, preventive vaccines for COVID-19 for vulnerable populations. The CVI has developed an approach that simultaneously advances the development of COVID-19 vaccines in aging populations and LIMCs, while laying the foundation for accelerating the development of vaccines and therapies for future emerging pathogens. The CVI works in two interconnected areas:

1. ***Protecting Vulnerable Populations***: The CVI will a) Define the course of COVID-19 disease in aging populations and LMICs, defining signatures of protection in natural infection, and prepare clinical sites to rapidly execute COVID-19 vaccine studies; and b) Evaluate the safety, host response and efficacy of experimental COVID-19 vaccines in aging populations and LMICs, facilitating global licensure and deployment. Such studies will couple systems biology and AI-driven bioinformatics to determine signatures of immunological protection in groups with sub-optimal immune responses. This in-depth analysis will provide the framework for prioritizing and improving COVID-19 vaccines and fill a critical gap in scientific knowledge required to address other diseases such as influenza, and future pandemics.

2. ***Translating Science to Policy:*** The CVI will ensure the development of evidence-based policy for COVID-19 vaccines. It will create a series of briefing to ensure that the major R&D challenges impeding the development of safe and effective COVID-19 vaccines for vulnerable populations are addressed, and will also serve as a neutral forum for dissemination and synthesis of critical information and data relevant to accelerating vaccine development and deployment.

The CVI leverages the **Human Vaccines Project's** world-class human immunology-based clinical research network, partnerships with major COVID-19 vaccine developers, and the **Human Immunomics Initiative**, a collaboration with the **Harvard T.H. Chan School of Public Health** focused on generating effective immunity in aging populations. This is supplemented with **FHI 360's** clinical capacity in more than 50 countries, **Aurum Institute's** capacity as one of the leading research centers on the African continent, and extensive COVID-19 policy expertise at the **Center for Infectious Disease Research and Policy (CIDRAP)** at the University of Minnesota.

As we have learned in the dramatic past few months, speed is of the essence in preventing and controlling pandemics. CVI will facilitate efforts of the global community to efficiently generate key information critical to

accelerating development of safe and effective vaccines against COVID-19 while providing a global blueprint for future pandemic preparedness for emerging infectious diseases. By accelerating development and access to vaccines—and anticipating future challenges -- we have the potential to save millions of lives.

Scientific Program

Cumulatively, CVI's scientific program addresses targeted and critical issues required to accelerate, evaluate and prioritize leading COVD-19 vaccines in key populations that historically have exhibited sub-par or diminished responses to vaccination. These critical studies will provide a blueprint for improving vaccines should first generation COVID-19 vaccines prove ineffective or marginally effective in these vulnerable population groups that make up a majority of the global population. Such work will also lay the groundwork for future pandemic responses by ensuring the development of vaccines that effectively protect vulnerable populations. CVI collaborators bring world-class expertise across systems biology, human immunology and AI/bioinformatics, combined with extensive experience studying aging populations and in the clinical evaluation of vaccines in LMICs. Work will take place in three interconnected components:

1. ***Natural History Studies***: Natural history studies will define the course of COVID-19 disease in aging populations and LMICs, define immunological signatures of protection in natural infection, and prepare clinical sites in LMICs to rapidly execute COVID-19 vaccine studies.
2. ***Vaccine Trials:*** Working with major vaccine developers, CVI will evaluate the safety, reactogenicity and immunogenicity of COVID-19 vaccine candidates in Phase 1b/2 studies across younger adults, elderly participants, and HIV-infected participants in LMICs. Studies will include extensive evaluation of immune and systems biological responses to vaccination to define predictive biomarkers of responders, which can then be evaluated in Phase 3 efficacy trials to help define correlates of protection. The CVI will also conduct novel immune modulation studies to improve the efficacy of COVID-19 vaccines, should data from first generation candidates prove to be suboptimal.
3. ***Centralized Immune Assessment and AI Laboratory***: Leveraging studies conducted in industrial settings and expanding upon laboratory infrastructure of HVP's collaborations with the Harvard T. H. Chan School of Public Health, the CVI will 1) Standardize laboratory assays and aggregate data to compare immune responses to vaccination across age groups in industrial and low income settings; 2) Apply AI and novel statistical techniques to evaluate signatures associated with COVID-19 disease progression and correlated of protection across populations; and 3) Provide technology transfer and capacity building to laboratories in LMICs.

These components are briefly described below:

1. **Natural History Studies.** Natural history studies are foundational components of the CVI, setting the immunological, epidemiological, and operational basis for rapid, efficient clinical trials of COVID-19 vaccines, while addressing central questions of immunity in vulnerable populations. Studies are planned to take place on three continents (Africa, Asia and South America) to establish clinical and immunological baselines for evaluating COVID-19 vaccines in older LMIC populations, while providing key information on SARS-COV-2 prevalence for the design of vaccine trials and selection of appropriate endpoints. Through in-depth systems biology characterizations of human immune responses to SARS-CoV-2, these studies will address immune variation across LMIC demographics and provide a baseline for comparison with data emerging from the US and Europe. Systems analyses will focus on virologic, human genomic, transcriptomic, metabolomic,

epigenetic and immunologic differences, with an emphasis on responses that can affect COVID-19 vaccine efficacy. In parallel at the same study sites, the CVI will conduct demonstration projects (see below- Vaccine Deployment Demonstration Projects) to recruit elderly uninfected participants to receive a licensed vaccine recommended for older persons, with baseline and prospective immunologic data collection. Critically, these studies will build capacity to enroll persons at risk of SARS-CoV-2 infection to rapidly implement COVID-19 vaccine studies in LMICs, and to test novel strategies for eventual COVID-19 vaccine deployment to adults and elderly in LMICs.

Study Details. CVI will conduct a multi-site prospective study to define the immune and systems biological profiles and clinical course of COVID-19 disease stratified by age (18-39, 40-59, 60+) and clinical stage (asymptomatic; exhibiting mild disease; having moderate disease; or severe disease requiring hospitalization). Study size across all sites is estimated at 600 volunteers total. Cohorts would have a balance of women and men and would include persons with HIV and TB. Clinical (including medication use) and immunological status will be determined at baseline and clinical outcomes and immune parameters ascertained during scheduled follow-up visits over 12 months, more frequent early and then three-monthly. Optimal clinical care will be provided consistent with emerging COVID-19 treatment guidelines, and active community outreach and linkage to COVID-19 testing and service providers will be conducted to identify and enroll the required samples per site.

Site Selection. Regions for study will be selected based on the evolving COVID-19 epidemic to begin work as COVID-19 is expanding, and likely include 4-6 sites in Africa, South/Southeast Asia and/or Latin America/Caribbean to allow for comparisons across geographies. Sites will be selected based on their demonstrated clinical research experience and their capacity to enroll both patients with COVID-19 disease and persons at risk for infection so that they will be ready to move seamlessly into COVID-19 vaccine trials as candidate vaccines become available. Various disease prevalence ratios will be taken into consideration for site selection including co-morbidities such as HIV infection, tuberculosis, other tropical diseases, and non-communicable chronic diseases that are common in LMIC populations.

Vaccine Deployment Demonstration Projects. Vaccine deployment to older persons is a challenge for health systems worldwide and is likely to be challenging for deployment of COVID-19 vaccines. CVI proposes to undertake multiple demonstration projects at the same study sites as above to test methods of deploying vaccines and recruiting older persons without acute illness for vaccine studies. Importantly, these studies will collect similar immunologic and systems biologic data on healthy elderly persons as the natural history studies do for persons with COVID-19. Site staff will collaborate with CVI staff to tailor recruitment and enrollment strategies to offer a licensed vaccine intended for those 60 years and over (e.g., shingles, influenza, pneumococcal). Here again, study size across all sites is estimated at 600 volunteers total, including women and men, including those on treatment for HIV and TB. Clinical (including medication use) and immunological status will be determined at baseline and immune parameters ascertained during scheduled follow-up visits over 12 months, with clinical care provided as needed.

Systems Analyses. Evaluation of COVID-19 natural history study participants will include complete clinical history; physical exam; chest x-rays and CT/PET scans where available; and collection of sputum and upper airway swabs for virus isolation and viral load determination. Laboratory testing will include a complete

blood count and chemistries; characterization of airway viruses, including SARS-CoV-2 viral load and genetic sequencing; the quality, magnitude and dynamics of the humoral immune response; and select cellular responses to SARS-CoV-2 infection across the spectrum of clinical presentation, from asymptomatic to severe disease. Sampling to support systems biology analyses in a specified subset of subjects would include genomic, proteomic, epigenetic, microbiome, metabolic and other assays. A central biorepository will be established to support biomarker and pathogenesis studies and to evaluate tests for SARS-CoV2. Some specialized assays will likely be conducted at reference laboratories in the HVP network, and planned capacity building and technology transfer will facilitate preparations for COVID-19 vaccine trials in LMICs.

Participants in the vaccine deployment and recruitment demonstration projects will undergo similar clinical and immunologic data collection, testing and specimen storage, without the detailed SARS-CoV-2 tests.

Site Standards. All sites will use standardized data collection, clinical, and laboratory procedures. Sites will develop community advisory groups and adhere to Good Participatory Practices (GPP). The study will adhere to Good Clinical Practices (GCP) and Good Laboratory Practice (GLP) guidelines. Participants will receive counselling and information on the study and provide written informed consent. The study protocol will be reviewed by local ethical review committees and one overall ethical review committee. Data will be managed at each site and pooled at a central data center. Standardized laboratory testing and immunologic assays will be conducted at each visit; technology transfer and training will be implemented to assure quality procedures. Clinical and laboratory specimens will be stored at each site with appropriate freezer capacity put in place.

2. **Vaccine Trials.** With clinical sites selected the CVI will partner with vaccine developers to rapidly test COVID-19 vaccines in elderly populations and LMICs. The CVI clinical program will have two primary components: 1) Phase 1b/2 vaccine studies for evaluation of the safety, reactogenicity and immunogenicity of the COVID-19 vaccine candidates in the elderly and LMICs to facilitate Phase 3 efficacy trials in LMICs and 2) Novel immune modulatory clinical studies which deploy a variety of approaches to enhance and modulate the effectiveness of existing vaccine through prime-boost strategies, modification of dosage and route of administration, adjuvants and other means of modulating immune responses for the elderly and those living in LMICs. Such studies will help to optimize effectiveness of vaccines for vulnerable populations.

   Phase 1b/2 Studies. Including elderly and LMIC populations in COVID-19 vaccine trials is essential to establish regimens that are safe and effective in vulnerable populations which may have suboptimal responses and where clinical endpoints may differ. COVID-19 vaccines that have successfully completed an initial phase 1 trial in an industrialized country, will be advanced for testing in the elderly and LMICs, and the CVI is already working with a range of product developers to ensure access to vaccines for proposed trials The proposed trials would be designed as Phase 1b/2 studies to evaluate the safety, reactogenicity and immunogenicity of the COVID-19 vaccine candidate(s) in adults, elderly participants and HIV- or TB infected participants. Primary objectives are to determine safety and immunogenicity in expanded populations. Secondary objectives are to compare immune responses with those observed in industrialized settings including systems biology analyses, to evaluate the impact of co-infections on safety and immunogenicity, to assess the occurrence of disease enhancement, and to prepare for phase 3 testing including confirming endpoint definitions. The proposed trials are designed to accrue data on ~1000

volunteers. These Phase 1b/2 studies are designed to prepare for and inform larger phase 3 efficacy trials with either individual or cluster randomized design which may require 5,000-10,000 volunteers per vaccine to estimate efficacy, depending on the choice of infection or disease clinical endpoint.

Study design will be a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial evaluating a two-dose regimen of the candidate vaccine administered at Day 1 and Day 29. Alternative boosting intervals can be accommodated depending on the candidate profile. Part 1 will enroll healthy adults, age 18-70, to receive low or high dose of the vaccine, in a 5:1 vaccine to placebo ratio. A Data and Safety Monitoring Board will review accumulated safety data from at least two weeks post-boost vaccination in all volunteers. Immunogenicity data accrued through four weeks post-boost will be used, together with safety data, to select a dose level to proceed to Part 2. In Part 2, enrollment will take place sequentially in adults 18-70 including those with co-morbidities, and HIV-infected adults.

Reactogenicity will be evaluated over 7 days after each vaccination and unsolicited adverse events characterized for 28 days after each vaccination. Serious adverse events and AEs of special interest will be collected throughout the study. All groups will be followed for 12 months after the last vaccination to accrue data on safety and durability of immunogenicity. Long-term follow-up for up to three years can be added in a separate follow-up protocol. The study design can accommodate addition of booster dose at 12 months that may be desirable in the endemic setting. Laboratory testing will be coordinated via a centralized laboratory which will ensure quality control at respective sites.

Immune Modulation Studies: A growing body of evidence suggests that immune responses to vaccination can be modulated and improved by a range of methods including prime-boost strategies, dose variation, route of administration (such as microneedles, intradermal, etc.), adjuvants and pre-vaccine modulation of baseline immunity through pharmacological interventions or anti-inflammatory modulators. Such approaches have potential to boost the impact of marginally efficacious vaccines, and better protect vulnerable subgroups with sub-par immune responses. Studies would be designed and tailored in the context of specific vaccine candidates.

3. **Centralized Immune Assessment and AI Laboratory:** With extensive systems biology analyses across natural history studies and vaccine trials, the CVI will generate massive data sets characterizing both immunological responses to natural infections and COVID vaccines across key demographics in LMICs. The laboratory will serve as a centralized facility to standardize laboratory assays and aggregate data to compare immune responses to vaccination across age groups in industrial and low income settings The CVI will conduct comprehensive analyses to provide a comprehensive blueprint of the mechanisms and signatures of effective immunity to COVID-19 infection and vaccines. Leveraging data sets from ongoing studies in industrial countries, the CVI will develop the first comprehensive and comparative assessment of immune responses between populations in high- and lower-income settings. Such work will provide essential insights in the evaluation and prioritization of existing COVID-19 vaccines, as well as foundational information to design more effective vaccines to combat future pandemics.

Advocacy and Policy Program

Scientifically rooted, evidence-based policy is essential for controlling and eventually ending the COVID-19 pandemic. Of importance will be ensuring policy measures that prioritize the development, selection and rapid accessibility of vaccines that protect vulnerable populations, particularly the elderly and those living in LMICs. With over 100 vaccine candidates in the pipeline, constraints on manufacturing capacity and limited experience in successful uptake of vaccines, policy makers will face significant challenges around vaccine development and deployment for vulnerable populations. To address these challenges, the CVI links some of the leading vaccine R&D specialists with pandemic policy experts in both industrialized and lower income countries to make complex information accessible. The CVI Advocacy and Policy program will be led by the **Center for Infectious Disease Research and Policy (CIDRAP)** at the University of Minnesota which has been at the forefront of pandemic preparedness for influenza and now COVID-19.

Advocacy and Policy. Inclusion of policy considerations to protect and ensure vaccine access for vulnerable populations (particularly in LMICs) has historically been overlooked in the context of pandemics. Furthermore, broad immunization programs advanced in LMICs over the last several decades have targeted routine immunization in children rather the full spectrum of those at risk in a pandemic including older adults. Pandemics such as COVID-19 present distinct challenges in terms of global equity, vaccine design, prioritization of products, appropriate clinical endpoints, manufacturing, financing, regulatory approval and harmonization, liability issues, community engagement and uptake, and affordability. In previous pandemics including the 2009-2010 H1N1 influenza pandemic, many of these issues were not considered until late in the pandemic, if at all, as high-income countries purchased most available vaccines for their own constituents.

To address these issues, the CVI will work with globally recognized experts in pandemic science and policy to develop a series of in-depth policy briefing papers on key topics in COVID-19 vaccine development and deployment for vulnerable populations, The initiative will be informed by connecting policy recommendations with COVID-19 R&D landscape analyses, and with emerging clinical and epidemiologic data including outcomes from CVI's studies. The CVI will also convene an external globally diverse Policy Advisory Group to guide and disseminate key policy recommendations. To help ensure effective and equitable policy outcomes, the CVI will leverage existing relationships and develop additional collaborations with major coordinating and implementation agencies and committees, including WHO, CEPI, GAVI and major governmental players where COVID-19 vaccine-related policy decisions will be made.

Communications. The CVI has begun implementing a coordinated communications plan to provide critical scientific and policy information around COVID-19 vaccine development to the global scientific and policy community. Such work includes: 1) the HVP COVID Report which distills the most important scientific and policy issues and data and reaches nearly 10,000 scientists and policy makers worldwide; 2) the Global COVID Lab Meeting where scientists openly present their latest data on COVID vaccine research; and is augmented by regular engagements by (10)(2e) Osterholm of CIDRAP on major news channels including CNN, MSNBC, PBS and others. As work expands in this area, the CVI will expand its public presence through the development of a web-based clearinghouse for comprehensive and transparent information around COVID-19 vaccine development (including key documents translated into other languages), the expansion of webinars to build support through stakeholder engagement, and virtual policy forums.

Estimated Budget

Area	Year 1[e]	Year 2	Year 3	Total[f]
Natural History and Vaccine Deployment Studies[a]	**$5.1M**	**$10.3M**	**$10.3M**	**$25.7M**
Vaccine Trials[b]	**$10M**	**$20M**	**$20M**	**$50.0M**
Central Immune and AI Laboratory[c]	**$3M**	**$6M**	**$6M**	**$15.0M**
Advocacy and Policy[d]	**$1.8M**	**$1.8M**	**$1.8M**	**$5.4M**
Total	**$19.9M**	**$38.1M**	**$38.1M**	**$96.1M**

[a] Assumes $18.5M for Natural History studies (n=600) and Vaccine Deployment demonstration projects. (N=600) conducted across 6 sites in LMICs; $15M for clinical sites ($2.5M per site); $3.5M for CVI science leadership, coordination, operations, and data integration with central immune and AI laboratory ; $7.2M for immunology and systems biological laboratory assays ($3K per subject; 2 time points).

[b] Assumes 1000 subjects for vaccine trials; Estimated at $50K per subject for clinical and laboratory studies, with laboratory assays conducted pre-immunization; one week post each immunization; plus 6 month and 12 months for durability of immunity analyses.

[c] Assumes costs for standardization of laboratories at each site, biorepository, data management, AI and machine learning, technology transfer and capacity building

[d] Assumes costs for advocacy, policy and communications

[e] Assumes 50% of costs in Year 1 for natural history and vaccine deployment studies and vaccine trials for start-up phases, with 100% of costs in Years 2 and 3; and 100% for advocacy, policy and communications in Years 1, 2,3

[f] Assumes Total (Direct + indirect) costs

About the Human Vaccines Project

The Human Vaccines Project is a nonprofit public-private partnership with a mission to decode the human immune system and accelerate the development of vaccines and immunotherapies across major global diseases. The Project brings together leading academic research centers, industrial partners, nonprofits and governments to answer core questions about how the human immune system fights disease and pioneer a new era in human health.
Learn more: https://www.humanvaccinesproject.org/

About FHI 360

FHI 360 is a nonprofit human development organization dedicated to improving lives in lasting ways by advancing integrated, locally driven solutions. Our staff includes experts in health, education, nutrition, environment, economic development, civil society, gender equality, youth, research, technology, communication and social marketing — creating a unique mix of capabilities to address today's interrelated development challenges. FHI 360 serves more than 60 countries and all U.S. states and territories.
Learn more: https://www.fhi360.org/

About CIDRAP

The Center for Infectious Disease Research and Policy is a global leader in addressing public health preparedness and emerging infectious disease response. Founded in 2001, CIDRAP is part of the Office of the Vice President for Research at the University of Minnesota.
Learn more: https://www.cidrap.umn.edu/

About Aurum Institute

Established in 1998, the Aurum Institute is an African Public Benefit Organisation whose mission is to improve the health of people and communities living in poverty through innovation in global health research, systems and delivery. It is rooted in Africa is dedicated to researching, supporting and implementing innovative, integrated approaches to Global Health with their headquarters in South Africa with offices in the USA, Ghana and Mozambique. The Aurum Institute has developed itself into a leading player, bridging the worlds of research, policy and implementation for impact.
Learn more: http://www.auruminstitute.org/

About the Human Immunomics Initiative

The Harvard T.H. Chan School of Public Health and the Human Vaccines Project established a joint project, the Human Immunomics Initiative (HII) that brings together Harvard Chan School experts in epidemiology, causal inference, immunology, and computational and systems biology with the resources and expertise of the Human Vaccines Project's human immunology-based clinical research consortium. HII will develop artificial intelligence-powered models of immunity that can be used to accelerate the design and testing of vaccines and therapeutics for a wide range of diseases. HII will specifically focus on determining the principles of effective immunity in aging populations, the world's largest growing demographic that has an immense disease burden and high morbidity and mortality in the current COVID-19 pandemic.
Learn more: https://www.hsph.harvard.edu/news/press-releases/human-immunomics-initiative-will-decode-immune-system-speed-new-vaccines/