OpenVax

OPEN SOURCE VACCINES FOR COVID-19 AND FUTURE PANDEMICS

VACCINES SOONER, SAFER, SURER, BETTER

An Armamentarium for Humanity

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Logline

Faster, safer, more accessible vaccines for COVID-19 and future pandemics, via repurposing existing, low cost, widely-available vaccines. Win the global vaccine race, more justly. Nonprofit venture. Phase 3 trials with top-tier players: Harvard, Government of India, ex-head of R&D for GlaxoSmithKline/former head of global health for Gates Foundation, Obama White House biotech expert, Mayo Clinic faculty.

Executive Summary

Fight COVID-19 and future pandemics rapidly and equitably by repurposing existing widely-available off-patent low-cost vaccines with strong safety records. Win the global vaccine race, more justly.

Counterintuitively, certain live attenuated vaccines protect against a broad range of pathogens, via the cutting-edge science of "trained innate immunity."

Compared to proprietary, monopolistic vaccine *candidates*, repurposed, low-cost, licensed *actual vaccines* have enormous scientific and economic advantages: *Sooner* – at **Phase 3,** on par with the ballyhooed leaders, but with huge advantages over them in distribution. *Safer* - **Well-established safety histories**, built over decades. *Surer* – There is no guarantee that a fully-effective proprietary vaccines will arrive, or be taken by the population. *Better* – they train the overall immune system, and **may be superior in preventing disease**; *Cheaper* – **~1000x** less costly to develop; *More Affordable* – prices as low as **eleven cents** per dose; *Combination* – can potentially be used **in combination** with proprietary vaccines, each potentiating the other. *Supply* – current distribution is **hundreds of millions to billions of doses per year**; IP is nonexclusive, and open to all countries and companies; *More Ethical Use of Public Funds* – **public funds for public IP, and free market competition among producers,** rather providing taxpayer dollars to private monopolies that have not guaranteed affordable pricing or open access to their research.

Launch multiple phase 3 COVID-19 vaccine clinical trials across an array of vaccines within weeks, perhaps more candidates than any other effort globally. Help create the field of vaccine repurposing, a new paradigm for pharma R&D, and an armamentarium for humanity. Nonprofit venture. Advisors include the former head of R&D at GSK/Takeda/Gates Foundation; infectious disease specialists at Harvard and the Mayo Clinic; biotech expert for the Obama White House; parties include Harvard Medical School, Government of India, and Open Source Pharma Foundation. Capital campaign: $10M – sufficient for testing and infrastructure to move not just one candidate, but an array of candidates, cohorts, and combinations through end of Phase 3 trials, and, if efficacy is found, through manufacturing and to start to reach the population at scale. Smaller increments are of concrete use as well—a single small Phase 3 trial for a single candidate has a remaining funding need of $500k, and small donations are of help too. A historic opportunity.

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Introduction

Simply put, we must save lives in pandemics - present and future. Time is of the essence.

The Open Source Pharma Foundation ("OSPF" www.ospfound.org) is a global nonprofit creating an alternate paradigm for pharma R&D, to develop medicine/vaccines for all, focused on repurposing for respiratory pandemics (tuberculosis, COVID-19, future pandemics), and nurturing a community. OSPF has years of experience in advocacy, open R&D methods, AI-based discovery, and clinical trials via generics repurposing. OSPF is already in phase 2B clinical trials for a respiratory pandemic. With partner the Government of India's National Institute for Research in Tuberculosis, it is exploring efficacy of metformin, a widely used off-patent diabetes drug with immunomodulatory effect, as an adjunct therapy for tuberculosis. OSPF has received financial support from the Tata, Wellcome, Rockefeller, and (pre-OSPF incorporation) Open Society philanthropies, and the Government of India. OSPF collaborates with Harvard, the Mayo Clinic, the Government of India, the US NIH, and others, and has been covered in the BBC, The Lancet, Fast Company ("How Open Source Medicine Could Prepare Us for the Next Pandemic"), and other publications.

OpenVax, the Pandemic Repurposing Venture ("Venture"), is led by OSPF in collaboration with trial leads the Harvard Medical School ("Harvard" https://hms.harvard.edu/) and the Government of India's National Institute for Research in Tuberculosis ("GOI" http://www.nirt.res.in/). The Venture leverages a global network of thought leaders, respiratory disease experience, open source philosophy/skillset, and repurposing expertise to nurture the discovery of effective, low-cost vaccines.

The Venture is close to launching **multiple Phase 3 COVID-19 vaccine trials** (phase 3 being a later stage than 90+% of COVID-19 vaccine projects globally), and perhaps more phase 3 trials than any other effort in the world, via repurposing existing approved vaccines selected for their demonstrated ability to protect against a broad array of pathogens. These safe and effective vaccines act via the cutting-edge, recently-understood concept of "trained innate immunity," and to a lesser extent, by exploiting viral homologies. At Phase 3, the Venture would be near the very front of the global vaccine race. Not only that, the Venture has additional huge advantages over the ballyhooed proprietary candidates in terms of safety track record, acceptability, affordability, and distribution. Although the scientific case for the Phase 3 trials leading to licensure is strong, the commercial potential is limited, creating a market failure.

The Venture is seeking to raise $10.0 million to fund a nonprofit venture to create the necessary infrastructure and to rapidly develop complete development of low cost vaccines for current and future pandemics, across an array of repurposing candidates, cohorts, and combinations. The bulk of the funding would be put to immediate use in accelerating phase 3 trials of COVID-19 vaccine candidates that ideally would reach the susceptible population within months.

If successful, such vaccines would be rapidly released, cost only a few cents per dose, avail of existing manufacturing capacity in the hundreds of millions of doses, and have intellectual property that is the "common heritage of all humankind."

The Venture also has potential systemic effect, helping forge a helping forge a new, faster, more scientifically driven, and more just path for pharma R&D. In a story of humanity versus the virus, the solution could be open source.

The Problem

The need for a COVID-19 vaccine is clear. Without one, the pandemic continues, killing and causing illness in large numbers, and disrupting lives and economies.

The Gap

As described below, the scientific case for conducting phase 3 COVID-19 vaccine clinical trials for certain repurposed vaccines is strong. However, as repurposed existing vaccines have limited commercial potential, funding is scarce, and R&D activity is too limited, relative to the health impact potential. Hence this nonprofit Venture, to accelerate, support, and fund vaccine repurposing R&D, across an array of candidate vaccines – perhaps the first effort globally of its kind.

Repurposed Widely Available Vaccines vs. Specific, Proprietary Vaccines:

Why use repurposed existing vaccines when pathogen-specific vaccines are well underway?

1) *Surer.* Vaccine R&D is difficult and uncertain. A fully-effective specific vaccine may never be developed, at least not in time to effect pandemic progression.
2) *Sooner.* As repurposed existent vaccines are already approved and in use, one can accelerate the development process, skipping directly to phase 3. If efficacy is shown, they could reach people within as soon as a few months from today, sooner than most or perhaps all *de novo* candidates.
3) *Safer.* The existing vaccines in question have been used by billions of people for decades, and strong safety records. They were also developed per rigorous standards, without shortcuts and rush.
4) *More Affordable.* The existing vaccines are distributed at a low price, as low as pennies per dose.
5) *Cheaper.* With sufficient basis, one can skip preclinical and phase 1, 2a, and 2b and go directly to phase 3; costs thus can be orders of magnitude lower. Rather than billions of dollars to take a single *de novo* candidate to the end of phase 3 trials, and, if efficacy is found, to manufacture it at scale, for $10M we can do this for multiple candidate vaccines.
6) *More Manufacturing.* Capacity to produce hundreds of millions of doses is already in place.
7) *Buys Time.* A repurposed vaccine could be used on a stop-gap or interim basis, until a specific vaccine is developed, as noted by the co-discoverer of HIV. We need something now. https://www.nytimes.com/2020/06/25/opinion/letters/coronavirus-vaccine-gallo.html
8) *Combination.* Specific and repurposed vaccines achieve different things and are complementary. Specific vaccines derived from sub-unit proteins may induce an antibody response but not necessarily strong innate immune or cellular immune responses which may be important in determining the severity of the consequences of infection. An ideal solution would provide not one but both, in combination. Note also that any specific vaccines – assuming they are approved – may not be fully effective.
9) *More Universal Access*. Even if a novel proprietary candidate works, who will have access? Likely not most people in Somalia or Cambodia, for example. Perhaps not even Arkansas or Illinois. What recourse will the lower-income 3 billion people have? Despite government funding, access questions remain unresolved.

10) *Future Pandemics*. Specific vaccines are costly and difficult to develop. Pandemics provide no luxury of time. In every pandemic, susceptible populations including critical health care workers will suffer as it waits for a specific vaccine. Repurposed vaccines can act against a broader array of pathogens; and can be an armamentarium for humanity, for this and future pandemics.
11) *Portfolio Approach.* As UK government has recognized, it is best to spread bets, and not rely solely a "star player." Most will not materialize, and the first may also not be the most effective.
12) *Against Vaccine Nationalism.* Should not a vaccine be available to all the citizens of the world?
13) *National Security.* And even as a matter of *realpolitik*, how can a country secure its future? It can try to get adequate rights to each and every single private proprietary candidate, and hope that even then that bigger or more inside players do not hoard the fruits, or it can back an open vaccine, which is nonexclusive, the common property of all humankind.
14) *Ethics of Public Funding.* In this situation, should public funds be going to subsidize private products over which the developer has a monopoly, particularly with no guarantees of affordable pricing or public data? Repurposed off patent vaccines, on the other hand, can be produced non-exclusively, by many parties, under conditions of market competition.
15) *Repurposing First*. In fact, some in the translational science community say that given the length and difficulties in *de novo* discovery, one should always start with repurposing.

Scientific Rationale:

Given the time needed and uncertainty associated with discovering a new specific vaccine, and the potential for combination use and interim use, not to mention the glaring access issues, OSPF has decided to explore repurposing existing vaccines. Many of the specific vaccine efforts use an approach akin to repurposing, with the main difference being that their work starts with a stalled vaccine candidate or platform from another virus, whereas OSPF is using a safe, well-known, successful vaccine.

Live Attenuated Vaccines & Trained Innate Immunity

Counterintuitively to the layperson, vaccines can be repurposed. For nearly 100 years, it has been known that an existing vaccine— specifically, a "live attenuated vaccine" using a weakened (or attenuated) form of the germ that causes a disease—can have "off-target" effects, providing a broad range of protection, beyond the pathogen it was originally designed to target. Researchers have continuously confirmed this phenomenon over the past decades, and recently unearthed how it happens.

By boosting and training the overall innate immune system, via the epigenetic modification of innate immune cells, including macrophages and natural killer cells, and through interferon mechanisms, certain live attenuated vaccines build a broad umbrella of protection against a wide range of pathogens - a response known as "trained innate immunity" [1] [25]. Trained innate immunity, and the potential of live attenuated vaccines against COVID-19, and the mechanism of action, was set forth in a September 10, 2020 article in the New England Journal of Medicine - "Trained Innate Immunity, Epigenetics, and Covid-19." [25]

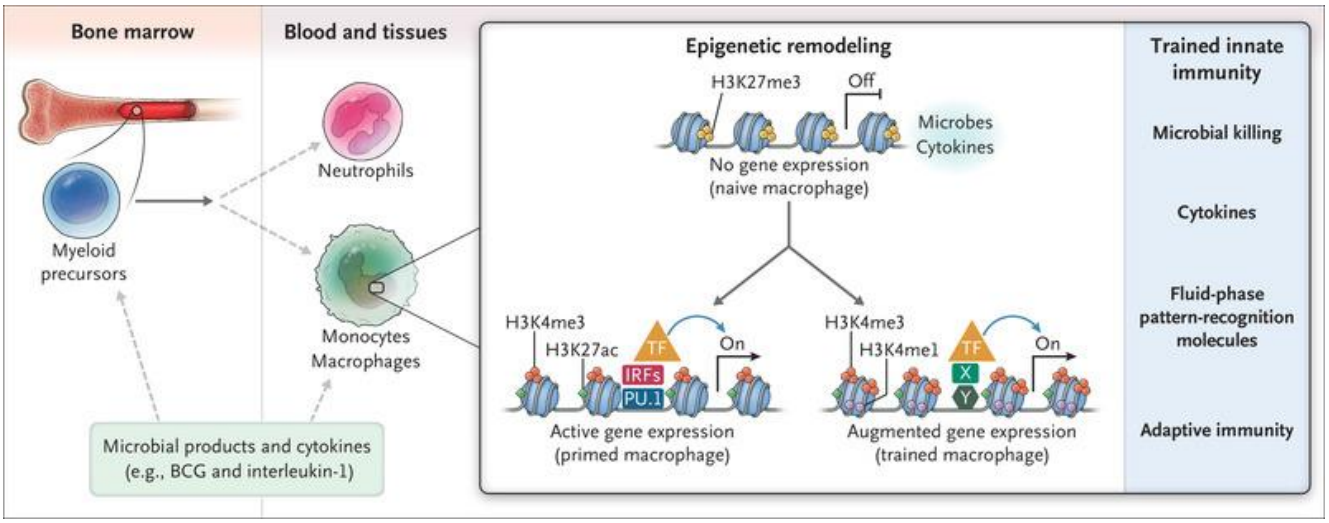

Figure 1. **Cellular and Molecular Mechanisms Underlying Trained Innate Immunity.**

Exposure to microbial signals, particularly from bacille Calmette–Guérin (BCG), and to cytokines trains myelomonocytic cells with enhanced effector function against microbial agents. Training can occur at the level of bone marrow hematopoietic stem cells or of mature macrophages. Training-mediated augmentation of myelomonocytic-cell function depends on reshaping of the epigenetic landscape driven at the level of stem cells by the pioneering transcription factor (TF) CCAAT/enhancer-binding protein β (C/EBPβ),[2] transcription of long noncoding RNA, and metabolic rewiring. Trained myeloid cells show enhanced killing capacity and increased production of cytokines, chemokines, and fluid-phase pattern-recognition molecules. Moreover, they are better suited to triggering adaptive immune responses. Training is likely to underlie the off-target pathogen-agnostic function of BCG and possibly other vaccines. Interferon regulatory factors (IRFs) and PU.1 are TFs. X and Y indicate TFs that are involved in the regulation of specific genes in trained macrophages.
Mantovani, A., Netea, M, Trained Innate Immunity, Epigenetics, and Covid-19. N Engl J Med 2020; 383:1078-1080
https://www.nejm.org/doi/full/10.1056/NEJMcibr2011679

Our focus is on a) live attenuated vaccines, b) which are already clearly shown to elicit "trained innate immunity," and thus to protect against a broad array of pathogens [2], c) which are already approved, off-patent, and in widespread use, and d) for which there is already evidence (e.g. lab/preclinical, related clinical, epidemiological) of promise against COVID-19. We do not claim now that these vaccines will protect against COVID-19, but the scientific case is clear that they are worthy of trial. Their effects wear off after some years, and so re-vaccination would be needed for those who have already received them. We hypothesize and seek to prove that these vaccines:

i. elicit "trained innate immunity" with protective effect against COVID-19 (either preventing infection or preventing disease progression); and/or
ii. exploit virus homologies (similar structure or physiology, or common ancestral lineage) with Sars-CoV-2

The Candidate Vaccines

The initial repurposed candidate vaccines are **BCG** (tuberculosis), **MMR** (measles/mumps/rubella) and **OPV** (oral polio vaccine). We are also evaluating additional candidate vaccines. A precis is below; detailed trial protocols and scientific rationales are available on request.

Concerning BCG, a review of the evidence supporting Phase 3 clinical trials of BCG against COVID-19, with over 100 scientific references, is available in Appendix D.[3] For nearly 100 years ago, it has been known that BCG has beneficial effects beyond tuberculosis prevention, now known as NSE's – non-specific effects.. In the 1920s, it was established that a reduction in overall child mortality – beyond TB – was associated with BCG. [4] It is now demonstrated, via nonclinical and clinical studies, that BCG provides protection against a number of infectious diseases apart from TB.[5] Effects include respiratory infections in children and adults, and in other viral infections. [6] A recent study in Greece, with results published in August 2020, showed nearly **45% reduction in *all* respiratory infections** among elderly people recently vaccinated with BCG, and a **79% reduction in respiratory infections of probable viral origin.** [7] Epidemiologic evidence shows significant associations between BCG vaccination and decreased COVID-19 deaths. [26] All of this makes the case for Phase 3 trials of BCG against COVID-19 very strong. The mechanism for this broad umbrella of protection, as described above, is "trained innate immunity. There is also ecological/epidemiological evidence that countries with BCG vaccination programs experience lower levels of COVID-19 deaths. [7] The effects of BCG do fade after a decade or more; hence the need for revaccination for more powerful impact.

Concerning MMR, there are four types of evidence supporting conducting clinical trials against COVID-19 - epidemiology, structure, mechanism, and clinical experience. First, the epidemiologic evidence. Much of the world receives MMR at childhood, and an unreviewed article concludes there is evidence to suggest that MMR is correlated with lower COVID-19 death rates. [9] Also at a population level., Franklin, *et al*, in a preprint, state that older populations and males are both more likely to die from COVID-19, but less likely to be seropositive for rubella-specific immunity, based on historical vaccination programmes. [10] Further, patients who have SARS-CoV2 infection had raised levels of rubella IgG to a level in keeping with secondary rubella infection. Second, concerning structure, there are structural similarities between SARS-Cov2 and the viruses targeted by MMR. Franklin *et al*, note that the SARS-CoV2 spike glycoproteins are class I viral membrane fusion proteins that share structural similarities with the fusion proteins from both measles and mumps viruses. [10] The macro domains of SARS-CoV-2 and rubella virus share 29% amino acid sequence identity. [10] Third, we have an idea as to mechanism. Anbarasu *et al* observe that vaccination may arrest the COVID-19 cytokine storm, as infections following MMR vaccinations have low levels of cytokine production. [11] They also note that MMR vaccine-induced interferon and NK cells are more potent and robust than those induced by wild-type disease strains. [11] Fourth, the clinical evidence. Fidel, *et al*, note that the vaccinations are given to all U.S. Navy recruits. Of the 955 sailors on the USS Roosevelt who tested positive for COVID-19, only one was hospitalized; this may have been a consequence of the fact that MMR vaccinations are given to all U.S. Navy recruits. [12] Fidel also notes that the US CDC has few contraindications against MMR in adults,and is even recommended for health care workers. In conclusion, noting commonalities between the MMR viruses and Sars-CoV-2 in transmission and their primary replication in the upper respiratory tract, as well as the cross-protective innate immunity offered by vaccination, Franklin *et al* suggest repurposing MMR against COVID-19 for both prophylaxis and preventing disease progression. Similarly, Fidel, *et al*, state that "a clinical trial with MMR in high-risk populations may provide a "low-risk–high-reward" preventive measure in saving lives during this unprecedented COVID-19 pandemic."[12]

Concerning OPV, the stimulation of innate immunity by live attenuated vaccines in general, and oral poliovirus vaccine (OPV) in particular, could provide temporary protection against COVID-19. [13] As both poliovirus and coronavirus are positive-strand RNA viruses, it is likely that they may induce and be affected by common innate immunity mechanisms. [14] Large-scale clinical studies in the 1960s and 1970s that involved more than 60,000 individuals showed that OPV was effective against influenza virus infection, reducing morbidity 3.8-fold, on average. [15, 16] OPV vaccination also had a therapeutic effect with regard to genital herpes simplex virus infections, accelerating healing. [14, 15]. In Bulgaria, mass immunization with OPV helped to control a 1975 outbreak of caused by Enterovirus 71.[16]

The Initial Trials:

Harnessing Sweat Equity

Harvard has been developing a Phase 3 trial for the most at-risk population for severe COVID-19 in the US, the elderly, with an initial network of sites in skilled nursing facilities (nursing homes) in Oklahoma. This study will use technology to reduce footprint and cost leveraging electronic medical systems in use across US nursing homes, and is nearing launch. The GOI has been developing its trials as well, and is launching two Phase 3 trials in India, amongst the elderly, and in health care workers. The detailed clinical trial protocols have been prepared and are available on request.

Distinctive Qualities

The trials have a number of interesting characteristics that separate them from the other repurposed and *de novo* vaccine trials.

Harvard trial: This is the first COVID-19 vaccine clinical trial of any kind to take place specifically in US nursing homes, even though nursing homes are where many of the most vulnerable are concentrated, and where a staggering 40% of US COVID-19 deaths occur. Further, the Harvard trial is the only COVID-19 vaccine trial in US nursing homes to explore nonspecific immunity, which is key to preventing disease progression. Lastly, the trial has death/severe disease as an endpoint. This is critical as vaccines should save lives; the trial measure should not merely be one of recovery time shortened by a few days. The PI is Professor Megan Murray of Harvard Medical School; the trial explores BCG.

GOI trials: The BCG/MMR head-to-head comparison would be unique globally. Further, BCG has scarcely been tried among elderly populations globally, and never in India. In fact, globally, most COVID-19 vaccine trials take place among the young, even though most deaths are among the elderly; indeed many protocols even exclude those who are older or who have co-morbidities. Lastly, further, India-specific trials are needed due to India-specific conditions (e.g. genetics, microbial infection history, regulatory, practicality - to launch to a billion people, one needs a trial in India). The PIs are GOI/NIRT's Dr Padma Priyadarshini and Dr. Subash Babu.

The table below summarizes the current status and capital needs of the current projects:

Phase 3 Trial Checklist:

Parameter	Harvard BCG Nursing Homes	GOI BCG Elderly	GOI BCG/ MMR Health Care Workers
Team (PI and others)	✓	✓	✓
Protocol Drafted	✓	✓	✓ (for BCG, MMR in process)
Regulatory and Ethics Applications Submitted	✓	✓	
Sites Identified	✓ (for ~50% of participants)	✓	✓
Vaccine Product Available	✓	✓	✓
Full/Partial Funding Commitment Received	✓	✓	
Remaining Funds Needed	$2M	Up to $200K	$400-$700K

Update – Aug 2020: Note that the Government of India BCG elderly trial has now been fully funded by the Government of India and has now commenced.

Economics, Distribution, Use of Proceeds, and Financing:

Given the limited commercial potential for repurposing, and an institutional bias toward novel purposing efforts despite the strong promise, OSPF seeks to raise capital for repurposing R&D from:

a. Governments, non-governmental entities and philanthropists (many fund *de novo* strategies)
b. Strategic partners, such as generic vaccine manufacturers that stand to benefit from an expansion of their markets, governments and health insurance companies who bear the expense to Covid-19 and respiratory infection treatment and companies/sponsors seeking brand benefits
c. Use of development prizes, advance market commitments, and contingent production contracts (awarded to parties who complete clinical trials successfully). These tools help reduce the development uncertainty and more clearly delineate a path to profitability for commercial partners

The vaccines would be open IP – “the common property of all humankind,” to draw from a famous phrase in international law, low cost, and avail of extant manufacturing and distribution in the hundreds of millions (BCG, MMR) to 1 billion (OPV) doses per year. [17, 18, 19]

As noted, R&D costs for repurposing approved vaccines are roughly 100x to 1000x cheaper than *de novo* discovery.

With regard to pricing, recent prices per dose (paid by UNICEF to private sector suppliers) are as follows: $2.85 for MMR, $0.11 for BCG, $0.015 for OPV [20].

With regard to use of proceeds, the bulk of the $10M raised would be put to immediate use, to accelerate and complete phase 3 clinical trials involving repurposed vaccines (the initial trials above, plus additional trials) across an array of candidates, cohorts, and combinations. The funds will also support infrastructure to work across the trials to facilitate cross-trial comparison; further establish the field of vaccine repurposing, which like drug repurposing may become an emerging and transformational area; build an open computational platform to accelerate vaccine R&D; and work to create equitable access to the fruits of pharma R&D. Smaller amounts, for fewer candidates and few trials and less infrastructure, are of use as well. As noted above, $2M is the remaining amount for the Harvard Phase 3 BCG US nursing home trial, and $500k for the Government of India BCG-MMR Phase 3 trial among health care workers.

The venture will go beyond COVID-19 and will fight other pandemics/public health scourges, as live attenuated vaccines that exhibit trained innate immunity protect across a broad spectrum of pathogens. While the full corpus sought will complete a slew of phase 3 trials, even a smaller quantum would complete one trial. This $10M will be enormously impactful – it will take *multiple* candidates all the way to the end of clinical trials, and if efficacy is found, through manufacturing and to large numbers of people. This is radically (100x to 1000x) more cost efficient than the billions required in standard *de novo* models to do just one vaccine, and faster as well.

For health care payers, such as insurance companies, an investment in this project would likely pay back, monetarily, many times over. A recent study showed a **45% reduction in *all* respiratory infections** among elderly people recently vaccinated with BCG, and a **79% reduction in respiratory infections of probable viral origin**.[21] These are dramatic results. In the US, every year nearly 8 million people aged 65 or older suffer from respiratory infections such as acute bronchitis, upper respiratory infections, influenza and pneumonia. [22] The total annual treatment expense of these ailments exceeds $14.5 billion. [23]. Even using the lower 45% figure, BCG vaccination among the elderly would reduce this annual expense by 45% of $14.5 billion, or $6.5 billion. The cost savings to a health care payer such as an insurance company or government would thus be substantial. For an individual private US health insurer, although the insurer would be in a far better position to calculate this, in a rough calculation, a one-time $10M investment in OpenVax would yield $32.5M in *annual* cost savings, for an annual return on investment of over 300%. [24] Given a P/E ratio of 10/1 (e.g. the ratio for CVS, the parent company of a major US health insurer), if cost savings become corporate earnings, this would translate into a $325 million increase in market capitalization.

For governments, an investment in OpenVax would have four main benefits – a) a better path to securing the health of its citizens, b) a more efficient use of public funds, c) more ethical use of public funds, and d) monetary savings in health expenditures. Without the OpenVax approach, a government faces a near impossible task. It must strike a deal with *every* single promising proprietary monopolistic candidate, provide public funds, and hope that the effort bears fruit, and that the bigger or more inside players do not hoard that fruit. A better, easier, and at least complementary approach, would be to create, for a tiny fraction of the cost, an open vaccine, for

which IP access is guaranteed, and manufacturing and distribution is more understood and robust.

In sum, we invite you to join the venture, regardless of your motivations: to be savvy, pursuing an approach that costs orders of magnitude less than standard models; to actually win the global vaccine race, and more equitably to boot; to exhibit foresight, fighting pandemics both current and future; to have an alternate plan for humanity, should the proprietary vaccines not arrive, or be less than wholly effective; to follow the ample scientific evidence, and fill an area of market failure; to go with a vaccine that billons have already used for decades and that has an ample safety history; to have a combination therapy, with proprietary and open vaccines acting in concert; to receive naming/title sponsor rights; to be affiliated with a project that will receive global media attention, and that will become a household name; to prove philanthropic bona fides; to learn from researchers; as a manufacturer, to benefit from an increase in demand for generic vaccines; as a health care payer, to save costs; to be science and health-driven, to participate in the cutting edge of a pharma paradigm shift; to participate in a concrete way in the idea of the oneness of humanity.

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Appendix A

Advisory Board

The venture is guided by an Advisory Board consisting of individuals with expertise in vaccine development, epidemiology, clinical practice, philanthropy, humanitarianism, and finance. The Board's Scientific Committee will be responsible for identifying and evaluating vaccine candidates. The Board's goal is to balance all factors and reach decisions that can create the greatest benefit for the widest swath of humanity's population. Major supporters will join the Board. The initial members of the Board include:

Tadataka (Tachi) Yamada, M.D.*
Tachi is currently a venture partner at Frazier Healthcare Partners where he functions primarily in new company creation. Before joining Frazier, Tachi was Chief Medical and Scientific Officer at Takeda Pharmaceuticals in Tokyo, as well as a member of the Board of Directors. Prior to Takeda, Tachi was President of the Bill & Melinda Gates Foundation Global Health Program in Seattle, where he oversaw over $9 billion in grants for applying technologies to address major health challenges of the developing world. Before joining the Gates Foundation, Tachi was Chairman of Research and Development at GlaxoSmithKline and member of the board of directors. Earlier, Tachi was the Chief of the Division of Gastroenterology and the Chair of the Department of Internal Medicine at the University of Michigan. In addition to his role at Frazier, Tachi serves as chair of the board of directors at the Clinton Health Access Initiative and has served as a member the President's Council of Advisors on Science and Technology and as Co-Chair of the Council of the National Academy of Medicine

Tachi received his M.D. from New York University School of Medicine and a B.A. in History from Stanford University. He has authored over 150 manuscripts in peer reviewed journals and is the editor of The Textbook of Gastroenterology. In recognition of his contributions to medicine and science he has been elected to membership in the National Academy of Medicine (US), the Academy of Medical Sciences (UK) and the National Academy of Medicine (Mexico).

Niranjan Kanesa-thasan, M.D., M.T.M.H.*
Niranjan Kanesa-thasan, M.D., M.T.M.H., FIDSA, FASTMH is the Chief Medical Officer of Icosavax and is a global medical executive with a successful 25-year career in vaccine research and development leading to seven licensed vaccines. He has extensive leadership and management experience in the biopharmaceutical industry (vice president, GSK Vaccines and Novartis Vaccines; Acambis, acquired by Sanofi Pasteur), government (Walter Reed Army Institute for Research, US Army Medical Research Institute for Infectious Diseases), and academia (Uniformed Services University of the Health Sciences, University Hospitals of Cleveland). His special expertise is in emerging infectious diseases and virus vaccines. Niranjan received an M.D. from the Johns Hopkins School of Medicine, a Masters in Tropical Medicine and Hygiene (MTMH) from the Uniformed Services University of the Health Sciences, and a B.A. from Johns Hopkins University. He completed residency training and chief residency in pediatrics and a fellowship in pediatric infectious disease and geographic medicine.

Megan Murray, M.D., D.P.H., M.P.H.*
Dr. Murray is the Ronda Stryker and William Johnston Professor of Global Health and Social Medicine at Harvard Medical School; Director of Research, Global Health & Social Medicine,

*Also on Scientific Committee of the Board

Harvard Medical School; and Director of Research at the Brigham and Women's Hospital Division of Global Health Equity and its sister organization, Partners In Health. She is also a Professor of Epidemiology at the Harvard School of Public Health where she leads a research team which conducts multidisciplinary research on MDR and XDR TB involving conventional and molecular epidemiology, cost-effectiveness and mathematical modeling, outcomes and operations research, and genomic epidemiology. She has conducted field studies in South Africa, Russia, Peru, the US, and Rwanda and has previously worked in Kenya, Niger and Pakistan. Dr. Murray serves as an editor for PLoS Medicine and for the European Journal of Epidemiology. She is a member of WHO's TB-STAG, the Stop TB MDR Working Group, and WHO Global XDR-TB Task Force. She has also served on numerous other committees including the Harvard University Human Subjects Committee, the University's Pandemic Flu Advisory Committee, the Institute of Medicine committee on Gulf War and Infectious Diseases and NIH study sections. Dr. Murray was instrumental in the development of a rapid diagnostic tool for Ebola, and her work on Cholera vaccination dramatically changed the global paradigm for use of the vaccine. Dr. Murray holds an MD, Master of Public Health, and Doctor of Public Health degrees, all from Harvard.

Michael Stebbins, Ph.D.

Dr. Stebbins is a geneticist, and public policy expert who served as the Assistant Director for Biotechnology in the Obama White House Office of Science and Technology Policy. He is currently the President of Science Advisors, a science and health consulting firm he founded in 2018 to provide science, technology, and public policy guidance to private companies, philanthropies, and non-profit organizations. While at the White House, Dr. Stebbins' work led to large initiatives across the Federal government to address antibiotic resistance, protect pollinators, improve veterans' mental health, increase access to federally funded scientific research publications and data, promote the preferential purchasing of antibiotic free meats, reform the regulatory system for biotechnology products, drive Federal purchasing of bio-based products, and improve the management of scientific collections. Dr. Stebbins previously served as the Vice President of Science and Technology for the Laura and John Arnold Foundation, science advisor to the Obama Presidential Campaign, and on the Obama White House Transition Team. He is the former director of biology policy for the Federation of American Scientists and worked for U.S. Senator Harry Reid and at the National Human Genome Research Institute. Before coming to Washington, he was a senior editor at Nature Genetics. Dr. Stebbins is on the Board of the Value in Cancer Care Consortium and chair of the Board for Vivli. He serves on the scientific advisory boards for Datavant and Amida Technology Solutions

Zelalem Temesgen, M.D.*

Zelalem (Zami) Temesgen is Professor of Medicine at the Mayo Clinic, in Rochester, Minnesota. An infectious disease specialist and a clinician, he works in HIV/AIDS, TB, and COVID-19. Dr. Temesgen treats COVID-19 patients, and is the Principal Investigator for three current COVID-19 clinical trials. Dr. Temesgen is part of the panel that reviews hospitalized COVID-19 cases at Mayo Clinic twice daily and makes recommendations on treatment. Dr Temesgen is also head of the Mayo Clinic Center for Tuberculosis, a WHO Collaborating Center in Digital Health and Precision Medicine for Tuberculosis. He holds his MD from Charles University, in Prague.

Jaykumar Menon, J.D., M.I.A.

Mr. Menon is an international human rights lawyer, scholar, and social entrepreneur. He is currently a Senior Fellow at the Harvard Global Health Institute, a Visiting Scientist at the Harvard School of Public Health, and a Research Fellow at the Centre for International Sustainable Development Law, which is based at McGill University. His research, teachings and practice focus on innovative approaches to realizing basic human rights for a billion or more people. He is a founder and the chair of the Open Source Pharma Foundation, which seeks to create an alternate

paradigm for pharma R&D, and develop low-cost medicines and vaccines in areas of great health need, and which is currently in Phase 2B clinical trials for a new adjunct therapy for tuberculosis. He is also a founder of The India Nutrition Initiative, which is developing salt double-fortified with iron and iodine ("DFS"), to help address the world's the most widespread form of malnutrition, iron deficiency, which afflicts 2 billion people, disproportionately women and children. DFS has been included in over 1 billion meals to date. Previously, Jaykumar led the international development program at the X PRIZE Foundation, an innovation group dedicated to achieving "radical breakthroughs for the benefit of humanity." As a human rights lawyer at the New York City-based Center for Constitutional Rights, he won a string of victories in high profile cases. His work includes representing student leaders of Tiananmen Square against the ex-Premier of China, helping win a $4 billion judgment on behalf of victims of the Bosnian genocide, freeing a man from death row in Indiana, helping represent the family of executed Nigerian environmental activist Ken Saro-Wiwa against Royal Dutch Shell ($15M settlement), and hunting through the prisons of New York for the real killer to help free an innocent man (David Wong) serving life for murder, as the 15th lawyer to take up the case. As a scholar, he has written articles in leading international human rights law journals and reference books. He has also co-founded a tech company with seven-figure revenues and worked as a strategist at McKinsey. He is a published creative writer. He is a life member of the Council on Foreign Relations, a finalist for Sweden's Tällberg Global Leadership Prize, and winner of the William Rogers Award, the Brown Alumni Association's highest honor, given to one graduate annually. Jaykumar holds a J.D. and a Master of International Affairs from Columbia University, along with a B.A. degree and one year of medical school at Brown. Through his creative and strategic approach, he hopes to achieve large scale and just change.

Nicholaos Krenteras, M.B.A.

Mr. Krenteras spent 14 years as a Partner and Managing Director of Pine Brook, a $6.7 billion AUM New York-based private equity firm. At Pine Brook, Mr. Krenteras was a member of the investment committee and board representative on numerous portfolio company boards. Prior to Pine Brook, Mr. Krenteras spent nine years in the financial services industry; working for LabMorgan, JP Morgan's financial technology venture capital arm, as vice president of portfolio development. Earlier in his career, he worked for Bank of America as an interest rate derivatives trader and as the vice president of trading and business development for Pedestal Capital, a start-up institutional brokerage for mortgage-backed securities. Mr. Krenteras holds an A.B. in International Relations from Brown University and an M.B.A. from the Columbia Business School, where he was a member of the Beta Gamma Sigma honor society.

Appendix B

Global COVID-19 Vaccine Repurposing Clinical Trial Landscape

(www.clinicaltrials.gov, accessed July 10, 2020)

Parameter	**BCG**	**MMR**	**OPV**	**Combinations** (Repurposed vaccine + specific preventive or therapeutic intervention)
Global COVID-19 clinical trials/ # (location)	15 (various)	1 (Egypt)	1 (Guinea-Bissau)	-
Participant focus (# of trials) (location)	Health care workers – 13 Elderly – 1 (Netherlands)	Health care workers – 1 (Egypt)	50+ years – 1 (Guinea-Bissau)	-

Appendix C

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Appendix D

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a) BCG vaccination reduces respiratory infections in the elderly by 45%, and by 79% for respiratory infections of probable viral origin (per the recent study published in Cell)

b) another trial confirms those findings, and BCG was adopted among the elderly,

c) per recent studies, the respiratory infection treatment expenditures for people 65 and above in the US are $14.5 billion, *every year*

d) those expenditures with BCG would be reduced by 45%, for a total expenditure savings of $6.5 billion,

e) each of the five largest private insurers US health insurers have roughly 5-12% of the private health insurance market in the US

f) by a rough and possibly conservative estimate, a single large private US health insurers would make not 5-12% but only 0.5% of health care expenditures for respiratory infections in the elderly (need to get more data on government vs private payers)

f) that same entity would receive a corresponding 0.5% of the savings in such expenditures

g) then that particular insurer would save 0.5% of $6.5 billion, or $32.5 million, *every year*

h) for an investment of $10M, that amounts to an annual return of over 300%.

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