

VACCINUUM

A Protective Layer for Humanity

Toward Universal, Open IP, Fast Acting Vaccines for All
People, to Shield Against SARS-CoV-2 and Variants,
Other Diseases, and Future Pandemics

Phase 3 Clinical Trials and Other Explorations



Bangalore – New York – Paris

VACCINUM

PROJECT SHORT TITLE: **ULTRA-BROAD SPECTRUM VACCINES**

PROJECT LONG TITLE: TOWARD UNIVERSAL VACCINES/ A PROTECTIVE LAYER FOR HUMANITY:
ULTRA-BROAD SPECTRUM OPEN SOURCE VACCINES TO PROTECT AGAINST SARS-CoV-2
VARIANTS, OTHER DISEASES, AND FUTURE EPIDEMICS - PHASE 3 TRIALS AND OTHER
EXPLORATIONS

Tagline: VVV: Vaccines for Virus Variants

Tagline: Vaccines of The People, by the People, and for the People

Quote from the Digital Citizen Community:

The big pharma vaccine development pipeline that takes out one or several variants at a time is a beautiful thing. But it should be combined with the complementary strategy of delivering public domain broad spectrum vaccines to the world. Whack-a-mole is good, but we also need a fence to keep the majority of the critters at bay.

Abstract: Most of the world has no access to the new, narrowly-targeted COVID-19 vaccines. Viruses mutate, become more virulent and contagious, and evade existing vaccines. And new pathogens emerge. To deal with these problem, this is a global social and scientific venture to create “ultra-broad spectrum” (UBS) vaccines, to protect all people against SARS-CoV-2 variants of concern, and against multiple diseases at once, and to stop future epidemics and pandemics before they start. The scientific advisory committee includes Prof. Robert Gallo, the co-discoverer of HIV, and Dr. Tachi Yamada, ex chair of R&D for GlaxoSmithKline, ex head of R&D for Takeda, and ex-President, Global Health, BMGF. Dr. Soumya Swaminathan, WHO Chief Scientist, is an Observer. The current generation of vaccines is designed to target only the adaptive immune system. Adaptive immunity is like a specialized spear. The spear takes weeks to develop, and works only against one pathogen, or certain variants of one pathogen. We plan to create a new generation of vaccines that also enhance the innate immune system. Innate immunity is like a broad moat; it protects against a wide range of pathogens and variants, known and unknown, at once. For rapid impact, our first focus is on repurposing existing off patent/low-cost vaccines in huge supply, with evidence of broad-spectrum protection, in some cases via decades of clinical trials, and testing them against SARS-CoV-2 variants. Initial projects include a Phase 3 vaccine trial against COVID-19 in Brazil set to commence in May 2021, and studies in South Africa and India. All are places where SARS-CoV-2 variants are of concern. Spreading globally, these variants have been shown to elude some new COVID-19 vaccines. Forging an alternate legal and economic model of vaccine development, some UBS vaccines could be made open source/open IP *ab initio*, and the “common property of all humankind,” available for non-exclusive production and broad access.

1. WHO IS INVOLVED

A. OSPF Scientific Advisory Committee:

1. Dr. Robert Gallo, MD. Co-discoverer, HIV; most widely-cited scientist in the world for a decade; Founder, Institute for Human Virology, University of Maryland School of Medicine; Co-Founder, Global Virus Network, leading global network of virologists. **(confirmed)**
2. Dr. Tachi Yamada, MD. Former Chair of Research & Development, GlaxoSmithKline; former President of Global Health, Bill and Melinda Gates Foundation, former head of R&D, Takeda Pharmaceuticals; Venture Partner, Frazier Healthcare. **(confirmed)**
3. Prof. Mihai Netea, MD, PhD. Radboud Univ, The Netherlands. Leading global expert in trained innate immunity, PI of several clinical trials in vaccine repurposing. **(confirmed)**
4. Prof. Zelalem Temesgen, MD, Professor of Medicine, Mayo Clinic, Infectious Disease Specialist, Director, Mayo Clinic Center for Tuberculosis **(confirmed)**
5. Dr. Gurusingham Sittampalam, PhD, Senior Advisor to the Director, US National Institutes of Health, National Center for Advancing Translational Sciences **(confirmed)**
6. Dr. Shaheed Jawahar, MD, MSc, former Deputy Director, Govt of India's National Institute for Research in Tuberculosis, a leading TB clinical trialist in India for 20+ years; OSPF advisor **(confirmed)**
7. Bernard Munos, MBA. Specialist in radical pharma innovation, 30 years at Eli Lilly; named one of 25 most influential people in biopharma globally; co-founder, OSPF. **(confirmed)**.
8. Dr. Stanley Plotkin, MD, Consultant and Emeritus Professor, Univ. of Pennsylvania. Helped invent rubella vaccine. Author of the leading global textbook on vaccines. Advisor on vaccines to Sanofi and others. Co-founder, Center for Epidemic Preparedness Innovation. (in our network, to be approached)
9. Prof. Megan Murray, MD, DPH, Professor, Harvard Medical School and Harvard School of Public Health (in our network, to be approached)
10. Prof Shabir Madhi, Professor of Vaccinology, University of the Witswatersrand, co-founder and co-Director of the African Leadership Initiative for Vaccinology Expertise (ALIVE). (in principle yes)
10. Dr. Jerome Kim, MD, Director General, International Vaccine Initiative, Seoul, Korea

(in our network, to be approached)

11. Dr. Ole Oleson, PhD, CEO, European Vaccine Initiative (in our network, to be approached)

12. Dr. Peter Small, MD, University of Washington (in our network, to be approached)

B. Others

1. Dr. Soumya Swaminathan, MD. Chief Scientist, World Health Organization. Observer. **(confirmed)**

C. Principal Investigators

1. Prof. Mihai Netea, MD, PhD. Radboud Univ, The Netherlands. Leading expert in trained innate immunity. <https://www.nejm.org/doi/full/10.1056/NEJMcibr2011679>; PI of several BCG trials. [https://www.cell.com/cell/fulltext/S0092-8674\(20\)31139-9](https://www.cell.com/cell/fulltext/S0092-8674(20)31139-9); [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31025-4/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31025-4/fulltext); Co-PI, Brazil Trial **(confirmed)**

2. Prof. Sergio Henrique Nascente Costa (Goias Faculty, Goiania, Brazil): Co-PI. **(confirmed)**

3. Prof. Michael Avidan, Washington Univ. School of Medicine, St Louis, USA. Global PI for CROWN MMR COVID-19 trial, <https://clinicaltrials.gov/ct2/show/NCT04333732> and five CROWN PI colleagues across South Africa - PIs, South Africa Trial **(confirmed)**

4. Prof. Shabir Madhi, PI, Professor of Vaccinology, University of the Witwatersrand, co-founder and co-Director of the African Leadership Initiative for Vaccinology Expertise (ALIVE). PI, South Africa Trial (in principle yes)

D. Sponsors and Partners

1. Partner: Global Virus Network, leading global network of virologists, with 66 institutional members in 34 countries. www.gvn.org

2. Sponsor and Project Leader: Open Source Pharma Foundation, a Southern-based global pharma R&D nonprofit. dedicated to medicine for all, with a focus on repurposing for respiratory pandemics. www.ospfound.org

2. EXECUTIVE SUMMARY

A. Introduction

SARS-CoV-2 virus variants of concern (VOCs) are a growing problem. They are more infectious than the original strain, and their prevalence is increasing rapidly. It is a matter of grave concern that some COVID-19 vaccines have been shown to be ineffective against VOCs. Finally, evolution favors the variants.

We must guard against a scenario where SARS-CoV-2 variants elude vaccines and ravage humanity. The downside risk is simply too high. It would be prudent, cost-effective, and even imperative, for the world to prepare a slate of universally accessible broad-spectrum vaccines to protect against variants. They could also prevent other diseases, and future epi- and pandemics, potentially even before they start.¹

To solve the problem, we can draw from a new paradigm in immunology. If the data from the proposed project bears out, we may be able to create what has long been considered a holy grail, and a moonshot, or even beyond that – an “ultra-broad spectrum” (UBS)² vaccine, which prevents many diseases at once, with the added advantage of being nearly universally accessible.

B. Two Paradigms in Immunology

The classical approach in immunology focuses on what is known as the adaptive immune system. This approach leads to the design of narrow vaccines which are highly effective against a very specific and original strain of single bacteria or virus, but which are perhaps not effective against their inevitable variants, let alone other diseases. This approach has been deployed with stunning speed for COVID-19, with massive credit owed to all involved, although huge issues of equitable access and hesitancy remain.

However, we are still playing a global game of catch-up: for every new epidemic or pandemic, a new vaccine will take roughly a year or more to develop, and additional years to distribute. And the variants bedevil, and may elude narrow vaccines. Further, other potentially preventable diseases go unchecked. In the interim, billions of people suffer, trillions of dollars are lost, and societies are locked down. The gap is too long and too costly.

The emerging paradigm favors breadth. Rather than narrow vaccines, can we create broad ones?

¹ Cf. “What Will It Take to Pandemic-Proof America?: When the next virus strikes, we’ll look back on this moment as an opportunity that we either seized or squandered” Dhruv Kullar, *The New Yorker*, April 15, 2021 <https://www.newyorker.com/science/annals-of-medicine/what-will-it-take-to-pandemic-proof-america>

² Many proposed broad spectrum or universal vaccines seek to protect against only multiple strains of a single pathogen. To define it precisely, an “ultra” broad spectrum (UBS) vaccine would: 1) protect against a single pathogen, and 2) protect against the variants of that pathogen, and 3) protect against many different pathogens and diseases at once 3) be usable in combination with narrowly-targeted vaccines, potentially yielding extended duration and increased efficacy 4) guard against pathogens that have not yet even emerged, and that are as yet unknown, allowing us to stop or curtail the next pandemic at the outset, or before it even starts.

The emerging paradigm in immunology focuses on what is called the innate immune system, that which defends across pathogens, and prevents many diseases at once. This cutting-edge science could, again if the data bears out, potentially enable a new and singular class of vaccines. Every vaccine in the world today - whether live-attenuated, inactivated, viral vector, mRNA, or other – is designed to target the adaptive immune system. This new class of vaccine would, by contrast, would target the innate immune system, which underlies broad spectrum protection.

C. Innate Immunity and Ultra-Broad Spectrum Vaccines

Is a UBS vaccine within reach? Though startling, our considered answer is yes. The latest peer-reviewed basic science research, published in authoritative journals such as the *New England Journal of Medicine* and *Cell*, elucidates the mechanism.³ Coupled with decades of clinical trial evidence, it tells us that a UBS vaccine is indeed feasible, and further yet, actually fairly well-established, respect to several non-COVID-19 diseases.

But first, a prefatory note. While the science and data are sound, the innate immunity-based approach is admittedly novel, so much so that it may require a sufficiently open scientific and industrial temperament to receive it. There may be something here that smacks of Thomas Kuhn's discussion of changing scientific paradigms. But of course, novelty, if founded, is the very basis of scientific advance. And although the analogy is imperfect, it may be worth remembering that synthetic mRNA approaches, now central in the vaccine landscape, were dismissed and unfunded for decades.⁴

D. Innate Immunity and Ultra Broad Spectrum Protection – Mechanism

So, as to the science: how exactly does this work? How can one vaccine prevent many diseases? Certain existing vaccines (the phenomenon is most well characterized to date in live attenuated vaccines, where a living weakened cell is injected into the body) activate and tune our overall innate immune system - a sort of protective moat that successfully handles the vast majority of infections during the course of in our lives – and cause it to bloom. This provides us with a fairly pathogen-agnostic, “off-target,” broad spectrum protection against many diseases at once. This sophisticated, powerful, and only recently-understood mechanism - systemic and almost symphonic in its operation, in contrast to the lock-and-key model of the classical vaccinology approach - is known as "trained innate immunity," as published recently in the *New England Journal of Medicine*, *Science*, and *Cell*, and described further below.⁵ In essence, some existing vaccines activate both the innate and adaptive immune systems, and may owe their broad

³ See, e.g. Mantovani, G. and 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>

⁴ <https://www.statnews.com/2020/11/10/the-story-of-mrna-how-a-once-dismissed-idea-became-a-leading-technology-in-the-covid-vaccine-race/>

⁵ See, e.g. Mantovani, G. and 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>

effectiveness to a synergistic effect. In sum, the body is a complex system, and by training and precisely stimulating our overall, natural, innate immune system - our first, fastest, most deeply evolutionarily-rooted, broadest, most frequently used, and most frequently successful line of protection – a vaccine can prevent many diseases at once.

E. Innate Immunity and Ultra Broad Spectrum Protection - Evidence

It has been known for nearly 100 years a live attenuated vaccine can prevent many diseases at once, reducing “all-cause” mortality.⁶ Decades of published clinical trials have borne this out.⁷ A recent pre-COVID clinical trial amongst the elderly of one such vaccine found a remarkable 79% reduction in *all* respiratory diseases of probable viral origin,⁸ which are a major cause of hospitalizations among the elderly. This would seem to merit large scale deployment among the elderly, or at the least additional large-scale studies. Merck even uses one of these vaccines, the BCG tuberculosis vaccine, as an approved therapy for bladder cancer, indicative of its broader effects.

With regard to COVID-19 in particular, the jury is out. There is some evidence of efficacy of certain existing vaccines from other diseases, via ecological studies, structural homologies, mechanism elucidation, and clinical reports, with results from small clinical trials emerging over the next year.⁹

⁶ Carl Näslund, a physician in Sweden, observed in 1927 a mortality rate three times lower among newborns vaccinated with BCG as compared those who did not have it. He commented: “one is tempted to explain the very low mortality among vaccinated children by the idea that BCG vaccine provokes a non-specific immunity.” Aaby, P. and C.S. Benn, *Saving lives by training innate immunity with bacille Calmette-Guerin vaccine*. Proc Natl Acad Sci U S A, 2012. 109(43): p. 17317-8. Similarly, Albert Calmette reported a four-fold decline in mortality in Romania in 1931. Calmette, A., Preventive Vaccination Against Tuberculosis with BCG. Proc R Soc Med, 1931. 24(11): p. 1481-90.

⁷ See, e.g. Chumakov., K, Benn, C. Aaby, P, Kottlil, S., Gallo, R. Can existing live vaccines prevent COVID-19?, <https://science.sciencemag.org/content/368/6496/1187.full>; Science 12 Jun 2020:Vol. 368, Issue 6496, pp. 1187-1188 DOI: 10.1126/science.abc4262 (focus on OPV – large clinical trials in the 1960s and 1970s showed that OPV was effective against influenza, and accelerated healing from herpes simplex infection); Higgin, et al, Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review,” British Medical Journal, 2016. <https://www.bmj.com/content/355/bmj.i5170> (“It is more than 30 years since early observational studies in west Africa suggested that some routine infant immunisations might have effects on risk of mortality and morbidity unrelated to the specific diseases they are intended to prevent.³⁴ Our review shows that many studies examining these non-specific effects of various vaccines have now been conducted and provides support for the hypothesis.”)

⁸ Giamarellos-Bourboulis, E.J., Tsilika, M., Moorlag, S., Antonakos, N., Kotsaki, A., Domínguez-Andrés, J., Kyriazopoulou, E., Gkavogianni, T., Adami, M.-E., Damoraki, G., Koufargyris, P., Karageorgos, A., Bolanou, A., Koenen, H., van Crevel, R., Droghiti, D.-I., Renieris, G., Papadopoulos, A., Netea, M.G., ACTIVATE: RANDOMIZED CLINICAL TRIAL OF BCG VACCINATION AGAINST INFECTION IN THE ELDERLY, Cell (2020), doi: <https://doi.org/10.1016/j.cell.2020.08.051>. [https://www.cell.com/cell/fulltext/S0092-8674\(20\)31139-9?rss=yes](https://www.cell.com/cell/fulltext/S0092-8674(20)31139-9?rss=yes)

⁹ If those trials come back with positive evidence, the case for UBS vaccines becomes of course much stronger. And in the meantime, it would still be prudent to act quickly to give ourselves all possible tools against variants, and

Concerning efficacy, while a UBS vaccine may not provide the same ninety plus percent effectiveness against a single pathogen as a narrowly-targeted vaccine, a UBS vaccine has myriad other advantages. It can a) still potentially be quite effective against a given pathogen, b) be used on a stop-gap basis, while a narrowly-targeted vaccine is being developed and distributed,¹⁰ c) be used in combination, to increase duration or efficacy, d) protect against a broader range of variants, pathogens, and diseases, and e) perhaps have longer duration, e.g. they may protect two years or more.

F. Brief Time Till Impact

Unusually, the basic science here is poised for rapid health impact. Typically, it takes several decades to move from basic science discovery to broad societal impact. Here, of course, we should try to create over the long term a new generation of novel vaccines that leverage innate immunity and provide ultra-broad spectrum protection. But to attain impact even more quickly, and to fight this pandemic, we can turn to existing vaccines from other diseases. Broad spectrum cross-disease protection via trained innate immunity is already known to be provided by a few existing, fully approved, off patent or low-cost vaccines that happen to also have widespread manufacture, distribution, and acceptance, with decades of safe use, and an existing reach of billions, with huge stockpiles, and which are ready for phase 3 clinical trials, cost as little as pennies a dose, and could reach much of humanity rapidly. These include the live attenuated vaccines of BCG, OPV, and MMR, as well as possibly yellow fever, and possibly other vaccines such as influenza and zoster.

Research and development in this promising area of trained innate immunity, despite its high health potential, is under-resourced. This is partly because it is a new and emerging avenue in immunology. And it is partly because of simple market failure, as the repurposing off patent or low price vaccines, a logical point of departure, provides insufficient ROI for large industry (which, apart from the government-funded COVID-19 efforts, has relatively limited investment in vaccines in the first place, given the short revenue streams).

G. Short Term Program

We propose here a program of basic science, product development, and eco-system creation. The program will be pathbreaking, and if the evidence generated bears out, world-changing. The effort will at very least accomplish a few large things: build the emerging paradigm of innate immunity; create a new field – that of vaccine repurposing, akin to the emergence of drug repurposing; and explore a new class and paradigm of vaccines, focused on the innate immune system.

also to try brand new interventions. Waiting and hoping that variants will not become a major problem is not a viable strategy; we must prepare .

¹⁰ “Doctor Robert Gallo: The Case for a Stop-Gap Vaccine” June 25, 2000
<https://www.nytimes.com/2020/06/25/opinion/letters/coronavirus-vaccine-gallo.html>

In the immediate term, we would begin with:

- a) immunological studies. Using blood samples, but not necessarily part of clinical trials, these would explore the use of repurposed vaccines against SARS-CoV-2 variants globally. The studies would also examine the pivotal question of whether various putative broad spectrum vaccines, given in combination with various tightly-targeted vaccines, enhance efficacy or duration of protection.
- b) phase 3 clinical trials. These would explore the efficacy of existing low-cost vaccines from other diseases that have already shown strong evidence of eliciting trained innate immunity and providing broad spectrum protection. We will conduct phase 3 trials in Brazil and South Africa, with a focus on MMR, influenza, and possibly others, exploring efficacy against the SARS-CoV-2 variants there. The variants are both widely prevalent and are known to escape the narrow vaccines.
- c) retrospective and observational studies. These would explore efficacy of the existing vaccines with broad spectrum potential, using extant massive clinical data sets.

H. Long Term Vision

The long-term project is to explore building an armamentarium for humanity, a sort of public-spirited and public-supported Manhattan Project. The ethical and scientific vision: a global protective layer, protecting all humans against pathogens known and unknown, comprised of broad-spectrum public domain vaccines. nonexclusively produced, and, to draw from the phrase in international law, the “property of all humankind.” Vaccines by humanity and for humanity, to cost-effectively and rapidly prevent a wide range of diseases amongst all humans, across ages, in countries rich and poor. Imagine a Martian looking down at the Earth, observing humanity under existential threat from a germ. Would they not expect the solution to be open source – developed rapidly and iteratively, by all working together, made by all, available to all? And even more so if it were funded from the public trough?

In more concrete terms, the long-term project involves conducting further basic science, and product development, and, as needed, work in adoption, partnerships, and awareness, seeking to create ultra-broad spectrum vaccines that are universally accessible (by virtue of being open IP or low cost, with large extant stockpiles and manufacturing). This might involve a large, global, adaptive clinical trial. One could even envision developing a novel, single, unitary, widely accessible vaccine that combines the broad spectrum aspects of multiple vaccines into one, a single vaccine that could protect against multiple classes of pathogens - coronaviruses, hantaviruses, and other infectious agents- including, wondrously, against pathogens as yet unknown and not yet emerged.

One might take inspiration from the Salk polio vaccine, which was as nearly important in its time as COVID-19 vaccines are today. The Salk vaccine was crowdfunded, patent free, and backed by

a pharma R&D nonprofit founded and run by New York lawyers, in a collaboration between Franklin Delano Roosevelt and Jonas Salk.¹¹

I. Practical Importance and Conclusion

If the effort is successful, how could these ultra-broad spectrum innate immunity-boosting vaccines be deployed? In five principal ways:

- 1) *Other Diseases.* We already have strong clinical trial evidence that certain vaccines protect off-target against non COVID-19 diseases—see the pre COVID ACTIVATE trial among the elderly in Greece, in which BCG vaccination reduced all respiratory infections of non-viral origin by 79%. Those are ready for deployment or at least further study.
- 2) *Bridge Vaccination.* In case of an epidemic or pandemic, such vaccines be rapidly deployed to providing partial protection, particularly to the vulnerable, to bridge the period until specific vaccines are developed. Here the creation of immunity within one hour (via innate immunity) rather than in two or more weeks (via adaptive immunity) becomes very important.
- 3) *Pre-Pandemic.* With, for example, booster shots of safe UBS vaccines every five years, or possibly even less frequently, pandemics could be curtailed or prevented from arising at all.
- 4) *In Combination.* Since the mechanisms are complementary, giving combinations of UBS and narrow vaccines might provide greater duration or efficacy than either type alone.
- 5) *One Vaccine to Rule them All.* In the long term, in addition to repurposing existing vaccines that elicit trained innate immunity, an important aim would be to design novel UBS vaccines that combine classical adaptive immune memory and trained immunity, to enhance even more strongly the immune response and to provide an improved broad protection.

Given the toll on humanity over the past year, the trillions in economic loss, or even the billions spent on vaccines to date, all of which is still mounting, this is a potentially high impact, high speed, orders-of-magnitude-less-R&D-cost element to add to our preventive portfolio. If we can complete well-founded phase 3 vaccine trials, coupled with widespread distribution, global accessibility, and broad acceptance, with variant protection potential, for a few million dollars, that is a worthwhile investment of trifling proportions.

And to put it bluntly, the cost of inaction is clear. For the next epidemic or pandemic, and to curb SARS-CoV-2 variants, and to prevent other diseases, we need broad spectrum vaccines. Otherwise, at each outbreak, we have may mass death and shutdowns for a year or more. Let us not repeat the experience of COVID-19.

¹¹ <https://slate.com/technology/2014/04/the-real-reasons-jonas-salk-didnt-patent-the-polio-vaccine.html>

3. CONTEXT

In a feat for the ages, industry fueled by government support has rapidly developed vaccines narrowly-targeted at the SARS-CoV-2 original strain. However, serious challenges remain for future pandemics, and for the remainder of this one.

- Virus Variants
 - SARS-Cov-2 variants are a growing problem; they are more infectious, and their prevalence is increasing rapidly.
 - Many of the new COVID-19 vaccines have been shown to have reduced efficacy against SARS-Cov-2 variants.
 - It would be prudent or even imperative to have a slate of vaccines that provide broader protection, to be ready should the variants situation worsen.
- Future Epi/Pandemics
 - It took >1 year for the narrowly-targeted vaccines to even start reaching people at scale. Although the work was heroic, in this fateful gap, trillions of dollars have been lost, and billions of lives affected by the SARS-Cov-2 virus.
 - Via ultra broad spectrum vaccines, we can respond at outbreak, or even potentially before, to prevent some epi/pandemics altogether.
- Global Equity and Justice
 - The new vaccines have mostly reached only wealthy nations. The majority of the world's population will not have access to COVID-19 vaccines for 1-2 more years. Repurposed vaccines could be an interim solution for vulnerable people who today have no options.
 - Several of the new COVID-19 vaccines require special cold chains, and are thus infeasible for widespread use in most low and middle income countries. With the ineffectiveness of the Astra Zeneca vaccine (which required no special cold chain) against the South Africa variant, and some discomfort around the Johnson and Johnson vaccine, low and middle income country options have become even more limited.
 - With off patent/public domain vaccines such as OPV, BCG, and MMR, the intellectual property is, already effectively open source, or, to draw from a phrase from international law, “the common property of all humankind.” Nonexclusive rapid mass scale production reaching billions is in place.
 - Note that this is perfectly compatible with commerce, and relies on

industry players to move things forward. (In another field, Big IT companies, once wary, are now major backers of open source software). Once the testing done, generic-type, low cost, and contract vaccine manufacturers can produce the vaccines on a commercial basis as they already do, selling billions of doses per year. And large pharma players, given the right financial incentives, can join in as well – note how Merck is now manufacturing the Johnson and Johnson COVID-19 vaccine.

- From a governance perspective, this would have taxpayer and philanthropic funds going, more appropriately, toward public and open IP products. It would avert issues stemming from public monies subsidizing proprietary monopoly products from private commercial entities.

- Vaccine Hesitancy

- A sizable percentage of people are reluctant to take the new COVID-19 vaccines. They should not be demonized. They fall into two major camps – those opposed to all vaccines, and those who have concerns about the new ones, particularly over their novelty, safety, and lack of long term safety track record. The latter group may be open to vaccines safely used by billions of children for over fifty years.

- Other Diseases

- Outside of the pandemic context, of course many diseases need prevention. The potential of broad spectrum vaccines – a field in its infancy – has not begun to be fully explored. As noted, in this clinical trial amongst the elderly in Greece published in *Cell*, the trained innate immunity-eliciting BCG vaccine reduced *all* respiratory infections of probable viral origin by an astounding 79%. [https://www.cell.com/cell/fulltext/S0092-8674\(20\)31139-9](https://www.cell.com/cell/fulltext/S0092-8674(20)31139-9)

- Speed

- Innate immunity-focused vaccines protect extensively within one hour, rather than the two weeks required by vaccines using the adaptive immunity-based approach. If the former were immediately deployed by a rapid response team at outbreak, they could alter the trajectory of or even quell a pandemic.
- The current new vaccines took nearly one year to develop, and will take years more to reach most of the world. In that gap the world shut down. Existing vaccines such as MMR, BCG, OPV, and flu, however, have already been developed and have some stockpiles, with immediate deployment possible, if

policy and evidence permits. (Generally, repurposed existing vaccines have huge speed advantages- they can skip right to phase 3 trials, and have manufacturing and distribution systems already in place.)

4. THE OPPORTUNITY

The emerging area of innate overall immunity, vaccine repurposing, and broad spectrum vaccines is in its infancy and we submit needs vastly more support.

a. Basic Science

In the basic science of immunology, a paradigm shift looms. Traditionally, the focus has been on what is known as “adaptive immunity”. We now see an increasing emphasis on “innate immunity.”

The downstream consequences of a focus on innate immunity are large. Rather than a goal of a vaccine which triggers only adaptive immunity and protects against one pathogen at a time, and an industrial plan that creates such vaccines singly and serially, as each germ or pandemic arises, we can now envisage ultra-broad spectrum “pan vaccines” that boost both types of immunity and can protect against many pathogens and variants at once, and which could even, although it might seem futuristic or farfetched, protect us against pathogens as yet unknown, and save humanity from the next pandemic immediately upon outbreak or even before it starts.

To explain how it works, with the help of analogies: Cutting edge research, grounded in an understanding of the complexity of systems, has underscored the importance and power of the innate immune system, which could be described as a wide protective moat, perhaps even full of crocodiles, that keep a wide array of invaders and creatures away from the castle. Adaptive immunity, on the other hand, is much more narrow, specialized, and targeted. It can be thought of as beginning with a guard in a tower, who must spot an invader and see their face and identify them by name. The guard then must inform colleagues in the castle armory, who over the course of two weeks design and manufacture a highly customized weapon that works only against that particular invader. That customized weapon will essentially work only against that single invader, and their identical twins and clones. It may not provide protection against the invaders’ siblings or cousins or children (i.e. variants), nor against other invaders from the same country, nor against invaders from a different land, let alone elephants or rhinos. In a nutshell, via innate immunity we can mount a broad defense, which precedes and complements adaptive immunity’s narrow counter-offense.

While both systems are very important, our somewhat un-sung innate immune system is what successfully responds to the vast majority of infections in our lives. When we fall ill with a cold, and have a scratchy throat for a few days, and then recover, that recovery is due to the workings of our innate immune system, which works against a wide array of infections. Our natural, general, innate immune system successfully neutralizes legions of pathogens within days, long

before our adaptive immune system, which needs two or more weeks to gear up and generate protection, ever kicks in.

Innate immunity may even be why such a large number of COVID-19 infections are asymptomatic. From an evolutionary perspective, 95% of species possess only innate immune systems, and do not have adaptive immunity. Although it may be too simplistic, bats, for example, fend off coronaviruses through their innate immune system, and bats do not appear – from what is known so far – to have been ravaged by the disease.

And now, via recent papers, we understand how our innate immune system can be trained and tuned to be even more effective – a process known as “trained innate immunity”.

<https://www.nejm.org/doi/full/10.1056/NEJMcibr2011679>. To continue the metaphor, trained innate immunity makes the moat fuller, and the crocodiles meaner and more plentiful.

At a mechanistic level, trained innate immunity works as follows. Certain vaccines, particularly live attenuated ones, train the innate immune system via improving macrophage and natural killer cell function, and possibly adjusting interferon mechanisms, with broad reaching effects. A brief description is here:

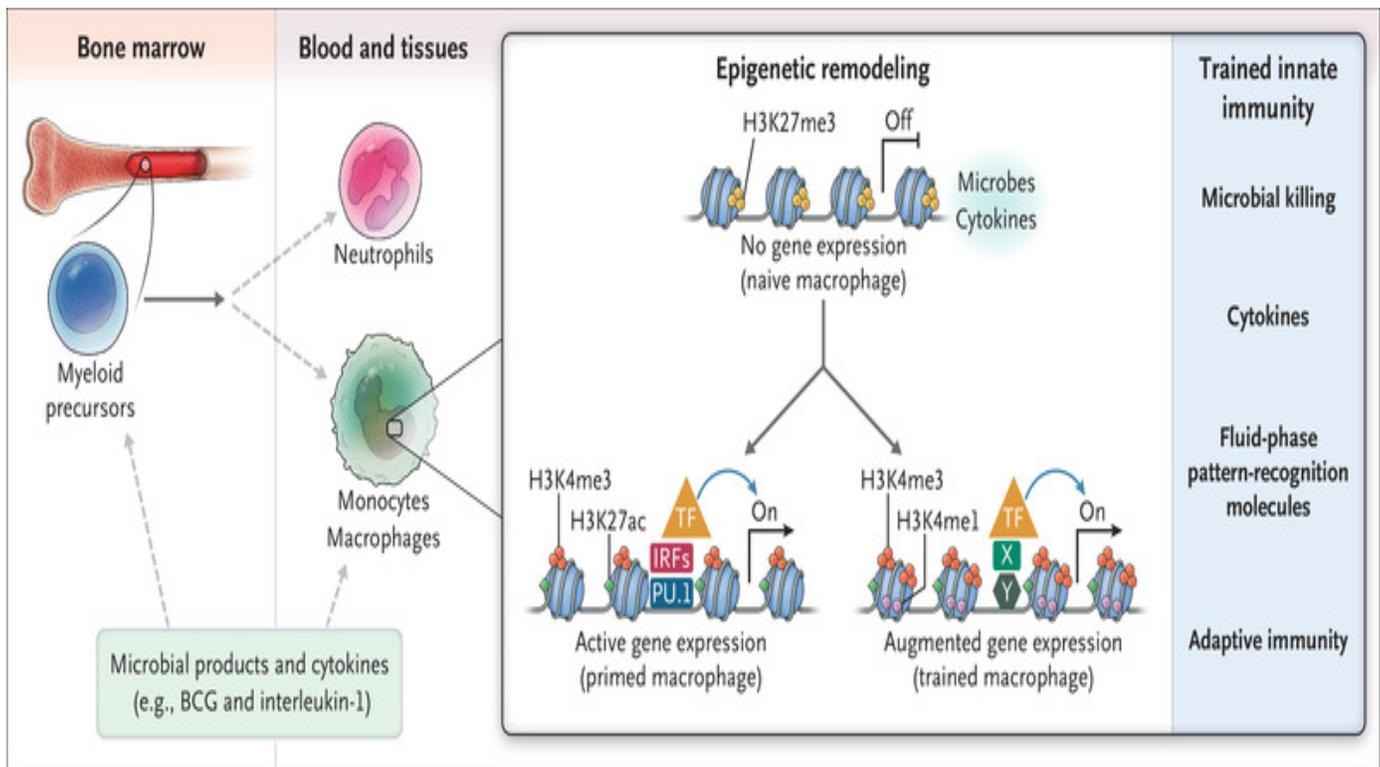


Figure 1. Cellular and Molecular Mechanisms Underlying Trained Innate Immunity.

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/EBP β),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.

<https://www.nejm.org/doi/full/10.1056/NEJMcibr2011679>

Mantovani, G. and Netea, M., Trained Innate Immunity, Epigenetics, and COVID-19, *N Engl J Med* 2020; 383:1078-1080.

In sum, if we can safely and strategically enhance our innate immune system, we will have a tool for immediate or even advance pandemic protection, and we might not need to repeat the pain that the world has been experiencing for the past year.

b. Cost and Speed

Certain existing, widely-available, approved, licensed, widely-accepted, non-exclusively manufactured, off-patent, live attenuated vaccines such as BCG (tuberculosis), MMR (measles, mumps, rubella), OPV (oral polio vaccine), and potentially low cost other vaccines such as flu vaccine, yellow fever vaccine, and zoster vaccine have been shown to elicit "trained innate immunity and may provide broad spectrum protection. They are extremely inexpensive, costing as little as pennies per dose.

The development process for repurposing existing approved vaccines, and simply using them unchanged against new diseases, can be years faster and orders of magnitude cheaper than for developing vaccines from scratch. In such repurposing, one can skip right to phase 3 clinical trials. And the process afterward is faster too, as enormous manufacturing and distribution capacity is already in place.

c. Universal Access: A Giant Leap for Humankind

With regard to existing off patent vaccines, their intellectual property is open --"the common heritage of all humankind", to draw from a famous phrase in international law. This supports universal access, via widespread, low-cost, nonexclusive production. Anyone who likes to, and who is qualified and meets regulatory standards, can make them. They are priced as low as pennies per dose. Billions of children worldwide, including in low income countries, receive vaccines such as MMR, BCG, and OPV every year, which is testament to their accessibility.

d. More Universal Acceptance

A sizable percentage of people are reluctant to take the new COVID-19 vaccines. They should not be demonized. They fall into two major camps. The first is opposed to all vaccines. The second is those who have concerns about the new vaccines. As noted, some of the latter group may be open to “tried and true” vaccines used by billions of children over a period of more than fifty years.

5. PROPOSED INITIAL RESEARCH AND DEVELOPMENT

a. Brazil

1. *Description*: Phase 3 Vaccine Clinical Trial. Three Arm Study: MMR, flu, placebo. Approximately 6000 participants (2000 participants per arm). Primary outcomes Moderate/severe COVID-19. Inclusion time: 2-3 months, follow-up: 6 months.
2. *Principal Investigators*: Prof Mihai Netea (Radboud Univ, Netherlands) (confirmed); Prof Sergio Henrique Nascente Costa (Goias Faculty, Goiania, Brazil) (confirmed)
3. *Status*: Ethics committee application submitted, small positive comments received. Basic trial is fully funded, with enrollment to commence in April or May 2021. Additional funds would help in accelerating progress, increasing robustness and power, adding immunology studies, and the like.
4. *Landscape*:
 - i. Presence: P.1 (Brazil) variant now spread to 25 countries.
 - ii. Vaccine Efficacy/Evasion: Reduced effectiveness versus P.1 (Brazil) has been shown *in vitro* for: Pfizer and Moderna vaccines (Beltran);¹² SinoVac vaccine (preprint);¹³ convalescent plasma, Moderna and Pfizer (David Ho group).¹⁴
 - iii. Prior Trials: No clinical trials to date of MMR or flu versus COVID-19 in Brazil.
5. *Ethics*. There is unfortunately currently little availability of the new, narrowly-targeted COVID -19 vaccines. Further, said vaccines may be ineffective against the Brazil variant, which is widely prevalent, and in any case no one will be barred or discouraged from receiving them. Those participating will have a chance at a remedy, and the society gains a potential new arrow in its quiver to deal with the

¹² W Beltran et al. <https://doi.org/10.1016/j.cell.2021.03.013>

¹³ De Souza, et al, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3793486

¹⁴ Shinde, V. et al. Preprint at medRxiv <https://doi.org/10.1101/2021.02.25.21252477> (2021).

pandemic. Further, if any of the vaccines being tested demonstrate efficacy, they will be made available to all participants in the trial who had not already received them.

b. South Africa studies

1. *Description:*

a. Immunology Studies

i. Examining immunologic effects of influenza vaccines on SARS-CoV-2 and variants.

ii. Examining human blood samples of variants *in vitro*, and testing efficacy against the variants *in vitro* vaccines, including vaccines from other diseases. Exploring the immunology of those who received the MMR vaccine and then later, for example, the Pfizer COVID-19 vaccine, versus those who received only MMR, or only Pfizer.

b. Phase 3 clinical trials repurposing existing vaccines against SARS-CoV-2 variants.

i. Expand existing BMGF-funded global CROWN Phase 3 MMR (measles-mumps-rubella) vaccine/COVID-19 trial, which has several centers in South Africa. Trial currently has about 2,000 participants enrolled. Could expand MMR arm to 20,000 participants, the higher power will yield more robust results, and/or add another arm. Trial commenced recruiting in earnest in Dec 2020; South Africa variant was first reported in December 2020, from an October 2020 sample. If we say that the variant was likely widespread by December 2020, that means the CROWN trial is exploring efficacy of MMR against the South Africa variants.

ii. Effectiveness of influenza vaccine. Possible trial.

2. *Principal Investigators:* Shabir Madhi and Marta Nunes, Wits University, Johannesburg (in principle yes), for influenza immunology and possible Phase 3 trial; Michael Avidan, Washington University, USA global PI of BMGF-funded CROWN MMR trial, and South Africa CROWN PI colleagues (confirmed), for MMR+ narrow vaccine immunology and expanded phase 3 trial.

3. *Status:* CROWN MMR trial as noted is ongoing; expansion in numbers is possible, as are additional arms. Protocols for Wits studies being prepared.

4. *Landscape:*

i. Prevalence. The B.1.351 or 501Y.V2 (South Africa) variant emerged around October 2020. It has been reported in 70 countries and overseas territories so far, including 16 countries in Africa.¹⁵ In South Africa, its prevalence was 94.5% during the Johnson and

¹⁵ https://cov-lineages.org/global_report_B.1.351.html

Johnson clinical trial, and 92.7% during the Novavax trial, and 92.9% during the Astra Zeneca clinical trial.¹⁶

ii. Vaccine Efficacy/Evasion:

- a. Negative results/prospects. Clinical trials showed that the Astra Zeneca vaccine was ineffective against the B.1.351 (South Africa) variant¹⁷, and that the Novavax vaccine had limited efficacy. In vitro testing found that the Pfizer and Moderna vaccines had limited efficacy.¹⁸ Pfizer and Moderna's vaccines use mRNA technology and thus need very cold temperatures for storage and are not widely distributed in low and middle income countries due to reasons of infrastructure and cost.
- b. Positive results. The Johnson and Johnson vaccine showed efficacy.¹⁹ Pfizer's Phase III clinical trial's South African arm showed 100% efficacy in a small number of Covid-positive cases (6 in the placebo vs 0 in the vaccine group).²⁰

iii. Other Trials. The CROWN MMR COVID-19 trial is recruiting in South Africa, with over 2,000 patients enrolled; a higher enrollment and more immunology studies would generate a more robust result, with more cases of severe disease. Most have been enrolled from December 2020 onwards, thus this trial is effectively testing efficacy against the South Africa variant. The same is likely the case for the ongoing BCG trials in South Africa. There have been no trials of an influenza vaccine against COVID-19 in South Africa.

5. *Ethics*. The new narrowly-targeted COVID-19 vaccines are unfortunately not yet

¹⁶ <https://www.fda.gov/media/146217/download>
<https://www.medrxiv.org/content/10.1101/2021.02.25.21252477v1>
<https://www.nejm.org/doi/10.1056/NEJMoa2102214>

¹⁷ A double blind randomized clinical trial in South Africa showed that the 2-dose ChAdOx1nCov-19 vaccine (Astra Zeneca) did not protect (10.4% efficacy (CI: -76.8 to 54.8)) against mild and moderate covid-19 disease caused by the B.1.351 variant (the trial only included young people without comorbidities so no severe cases in the placebo group either)

¹⁸ When Pfizer vaccinee sera was tested against that B.1.351 live virus strain, the neutralizing capacity was significantly lowered to varied amounts in different studies (14 fold in an Institut Pasteur study, 10.4 fold in a Columbia University (David Ho) study, 7.6 fold in an Oxford University study, and 6.8 fold in a pseudovirus based study by an Israeli Institute)

<https://www.nature.com/articles/s41591-021-01318-5>
https://www.nature.com/articles/s41586-021-03398-2_reference.pdf
[https://www.cell.com/cell/pdf/S0092-8674\(21\)00226-9.pdf](https://www.cell.com/cell/pdf/S0092-8674(21)00226-9.pdf)
<https://www.sciencedirect.com/science/article/pii/S1931312821001360>

¹⁹ A double blind randomized clinical trial by J&J in South Africa showed a 64% efficacy in preventing mild to moderate to severe/critical Covid and 81% efficacy in preventing severe/critical cases, with disease onset at least 28 days after the vaccination.

<https://www.fda.gov/media/146217/download>

²⁰<https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-confirm-high-efficacy-and-no-serious>

widely available in South Africa. The CROWN and other trials have ethical approval and are recruiting.

6. *Status*: CROWN trial is established and ongoing and is willing to expand the number of participants to make it a higher-powered study. Note that the Southern hemisphere winter approaches, and we may see heightened waves of infection for both Brazil and South Africa.

c. Create program in and launch field of innate immunity / vaccine repurposing

1. *Immunologic studies*

Examine anonymized blood samples, drawn from patients. This is much simpler and cheaper than mounting a full clinical trial. We envision samples in Brazil and/or South Africa, but also perhaps in other locations -e.g. the US, Ghana, and India. The samples come from i) people without COVID-19, ii) people who have the original strain of the SARS-CoV-2 virus, and iii) people who have a variant. With those samples, we will examine the workings of various novel and repurposed vaccines. We will also analyze samples from individuals who have taken a potential broad spectrum vaccine, such as MMR or BCG, and then several weeks later have also taken a narrowly-targeted COVID-19 vaccine, such as Pfizer or Astra Zeneca; the studies will explore if the vaccines acted synergistically or negatively. More specifically, they will examine whether the putative broad spectrum vaccine increased the efficacy or duration of the narrowly-targeted vaccine. If the duration of protection of the new COVID-19 vaccines, for example, were increased, this would have worldwide implications.

2. *Develop Additional Clinical Trials*

- a. Conduct expanded version of the ACTIVATE elderly study.
[https://www.cell.com/cell/fulltext/S0092-8674\(20\)31139-9](https://www.cell.com/cell/fulltext/S0092-8674(20)31139-9)

Clinical trial found that recent BCG vaccination for elderly in Greece reduced incidence of *all* respiratory infections of probable viral origin by 79%. Such infections cause a large fraction of hospitalizations among the elderly and high health care expenditures, with consequences even for insurers. If needed, this could be done in a large, high-powered, global study.

- b. Explore OPV repurposing trials

- c. Create linkages for a global adaptive trial – e.g. with WHO Solidarity or other global clinical trial networks.

3. *Partnerships*

- a. Explore non-traditional and non-OECD funding sources

- i, Governments: For example, with the African Union, or with the

Government of Kerala, India, where we have strong ties.

ii. Industry Communities: Wall Street and Silicon Valley

iii. Crowdfunding

iv. NGOs and citizen's associations

a. Rotary or Kiwanis, which work in public health

b. March of Dimes. – MoD helped create the crowd-funded, patent free, Salk polio vaccine.

4. Help Create New Field - Vaccine Repurposing.

a. Hold conferences and seminars

b. Build data repositories.

c. Create AI-powered open knowledge graph for vaccine repurposing, along the lines of OSPF's TB knowledge graph

d. Conduct retrospective studies on large clinical datasets – e.g. potentially Univ of California (via Chief Data Officer Prof. Atul Butte, M.D.), U.S. Veterans Administration, France/INSERM.

5. Results Dissemination

6. Awareness, Advocacy, Access, Coordination

In addition to science, this effort will require a significant amount of glue and connective tissue, including the following: coordination; communication with academia, government, industry, and the public; scientific advisory board coordination; results dissemination; advocacy as needed; work on manufacturing, distribution, equity, and access; and overall championing. And one must be prepared: if the results of any of the repurposed vaccine trials are positive, there will need to be major work done to explore and facilitate adoption and move them into deployment, and there will be no large company to drive this effort as is the case with the proprietary vaccines.

7. Initial work on long term research and disease prevention agenda, which is described below.

5. LONG TERM RESEARCH AND DISEASE PREVENTION AGENDA RE INNATE IMMUNITY AND VACCINE REPURPOSING

- a. Global adaptive trial with high power
- b. Basic science studies
- c. Retrospective and observational studies
- d. Explorations of combinations and complementary approaches (e.g exploring two broad spectrum vaccines given in combination, or a broad spectrum + specific vaccine,
- e. Explorations of a novel “pan vax” – not repurposing, but a new single vaccine that could protect against many classes of pathogens at once
- f. Knowledge Dissemination
- g. Adoption/Enabling Public Health Strategies (e.g. vaccination at outbreak, to vulnerable populations; as interim measures for epi/pandemics, while specific vaccines are being developed; in advance, as possible booster shots, to prevent diseases or epi/pandemics before they start). Moving from completed scientific study to on the ground reality.

6. OPEN SOURCE AND HUMANITARIAN ELEMENTS

- a. Legal research and drafting: Drafting of open IP /humanitarian licenses for the repurposed vaccines.
- b. Open Source Elements to Clinical Trial Methodology: If possible and if all the parties are amenable: open commentary on clinical trial or other study protocols, open commentary on survey instruments, open enrollment techniques, open anonymized full trial data.

7. LIST OF APPENDICES

- A. Research Synopses, Protocols, and Other Documents
- B. Party Information