13D GLOBAL STRATEGY & RESEARCH

WHAT I LEARNED THIS WEEK®

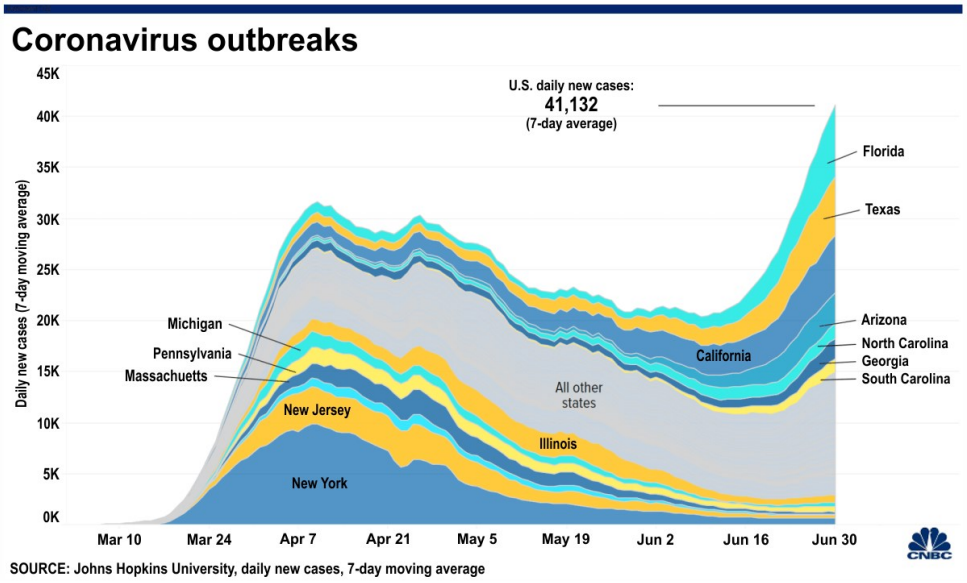
Excerpt from July 2, 2020

COVID-19 outbreaks are multiplying and immunity may be short-lived. Could existing "live" vaccines, which stimulate innate immunity, outshine vaccines targeting the "spike" protein?

Jul 02, 2020

This week, America has repeatedly hit daily highs of over 40,000 confirmed new infections. The cases are being led primarily by huge outbreaks in four states: Florida, Texas, California, and Arizona.

In Texas, the percentage of people testing positive for SARS-CoV-2 has soared from 4% to over 13%. **Phoenix is now seeing more new cases per day than New York City's boroughs did at their worst,** notes *The Washington Post*. Arizona now has more cases per capita than any country in Europe or even Brazil.



Source: CNBC

This week, Dr. Anthony Fauci warned that America could soon record 100,000 new cases of COVID-19 per day unless the trajectory is changed.

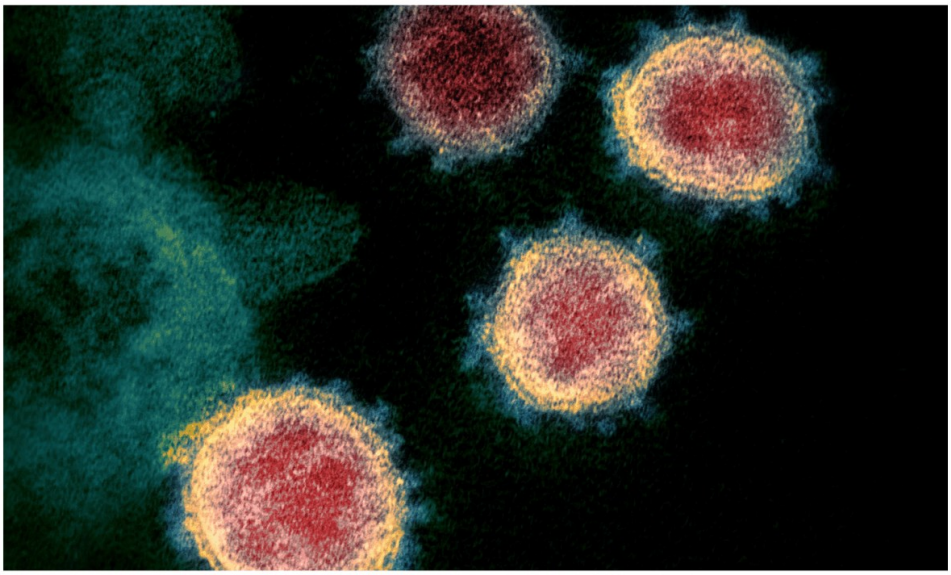
Recently, we spoke with Dr. Robert C. Gallo, M.D., one of the world's leading virologists. **Dr. Gallo believes that existing "live" vaccines for other infectious diseases, such as polio, tuberculosis, measles, and smallpox, could be repurposed to provide temporary protection until a more specific COVID-19 vaccine is developed.**

In 1984, Gallo co-discovered that the HIV virus was the cause of AIDS and developed the HIV blood test. In 1996, Gallo was heralded for one of that year's most important scientific breakthroughs when he discovered that natural compounds, called chemokines, **can block HIV and halt the progression of AIDS.**

Dr. Gallo currently runs The Institute of Human Virology (IHV), which he co-founded in 1996, as part of the University of Maryland School of Medicine. In 2011, Dr. Gallo co-founded the Global Virus Network (GVN), which aims to help the world respond rapidly to new or re-emerging viruses. *Presently, GVN holds virtual group meetings every 10 days sharing breakthroughs and insights on COVID-19 treatments.*

Dr. Gallo warns that antibodies associated with coronaviruses typically only last four to five months, suggesting that any protection they provide is minimal. A new Chinese study published in *Nature Medicine* found antibody levels in recovered COVID-19 patients fell sharply within two to three months after infection for both symptomatic and asymptomatic patients. *For 90% of patients, the median percentage decrease was over 70%.*

A major risk to the world's current vaccine strategy, in Gallo's view, is that all (or virtually all) of the approximately 160 COVID-19 vaccines in development are going after the "spike" structure on the SARS-CoV-2 virus. Gallo warns that we won't know about the latent effects from the vaccines nor durability of antibodies for about a year after clinical trials are completed. Gallo recently wrote in the *New York Times*: **"What's Plan B if the antibodies to the spike protein are not durable or if the spike protein mutates, as has been seen in some studies?"**



A transmission electron microscope view of the coronavirus. Photo: Image Point FR/LPN/BSIP/Universal Images Group via Getty Images

Source: Getty Images via Axios

"Live" vaccines induce broader protection against unrelated pathogens, likely by inducing interferon and other innate immunity mechanisms, notes Gallo and colleagues in a recent analysis in *Science*. "Live" vaccines provide a stronger immune response, as they use a weakened form of the germ that causes a disease. Live vaccines train the body's immune system by initiating changes in some stem cells. **Live vaccines also stimulate "viral interference" and create tiny marks that help cells turn on genes involved in immune protection against multiple pathogens.**

Researchers at over 25 universities and clinical centers worldwide have begun clinical trials of live vaccines to combat COVID-19. Patient studies are primarily being conducted on health-care workers to test if a live tuberculosis vaccine that has been used for 99 years, known as "Bacillus Calmette-Guerin" (or BCG), can reduce risks associated with COVID-19.

Dr. Gallo and Shyam Kottilil, Director of the Clinical Division at IHV and Head of Infectious Diseases at UMD School of Medicine, are also helping countries set up clinical trials to test the 60-year-old live oral polio vaccine (OPV). **The scientists believe OPV could provide eight to 10 weeks of protection, potentially longer, against COVID-19.** Both the poliovirus and coronavirus are positive-strand RNA viruses. *Therefore, OPV should activate the same common innate-immunity mechanisms.*

The human body's "innate immunity" system is different from adaptive immunity, which produces antibodies. **Innate immunology has become one of the hottest areas of research in epidemiology, underscores Gallo.** Over the last decade, immunologists have discovered that

live vaccines also stimulate the innate immune system, which is less specific but much faster than the adaptive immune system. The innate immune system is an emergency response by the human body.

The evidence for live vaccines has been building for decades. The first evidence came in 1927, following the availability of BCG, when Carl Naslund of the Swedish Tuberculosis Society observed that **children vaccinated with the live tuberculosis vaccine were three times less likely to die *of any cause* compared to those who were not inoculated.**

Numerous studies over the last 50 years show that live vaccines can also have a broad impact on other diseases. During the 1940s and 50s in clinical trials in both the U.S. and Britain, **scientists found that BCG reduced non-accidental deaths from causes other than tuberculosis by 25%,** on average.

During the 1950s, Russian scientists noticed that **people who had been given the live polio vaccine were far less likely to fall ill with the seasonal flu** and other respiratory infections. In response, Marina Voroshilova of the Academy of Medical Science in Moscow and other scientists launched a clinical trial for the impact of OPV on other infectious diseases, testing 320,000 Russians.

They found that in individuals who had been inoculated with OPV, "the incidence of seasonal influenza was reduced by 75%," notes Konstantin Chumakov, who is Voroshilova's son. Chumakov, a close colleague of Gallo, is now associate director for research at the U.S. FDA's Office of Vaccines Research and Review.

Large-scale studies of OPV for non-specific prevention of diseases were carried out during the 1960s and 1970s. The clinical trials involved over 60,000 people and showed that OPV was effective against influenza, reducing morbidity 3.8-fold on average. OPV also had a **therapeutic effect on genital herpes** simplex virus infections, accelerating healing. **OPV also showed oncolytic properties, by directly destroying tumor cells and activating cellular immunity toward tumors.**

The oral polio vaccine is a "sugar" pill that costs around 12 cents per dose. A billion doses are produced annually in over 140 countries and could very likely be scaled up within a few months. The existence of multiple serotypes of OPV also means that it could be used sequentially to prolong protection. OPV *produces herd effects as well when large portions of a population are vaccinated and could help prevent the spread of* SARS-CoV-2.

OPV is presently used in 143 countries. The U.S. no longer uses OPV, opting for an inactivated polio vaccine. A trial for the use of OPV against SARS-CoV-2 is presently underway in Russia. Iran is also planning a trial with all approvals received, the population ready to study, and procurement of 130,000 doses of OPV initiated. *Trials are also being considered in Guinea-Bissau, Indonesia, Mexico, Brazil, Uzbekistan, and India.*

In the U.S., efforts to hold a clinical trial for use of OPV against SARS-CoV-2 has been delayed. **"We believe this is very, very, very safe," says Dr. Gallo.** One out of every 2.7 million people receiving OPV can develop a central nervous system complication, but it is unclear that it is directly related to the vaccine, notes Gallo.

However, **if like most Americans, a person has already been vaccinated for polio with OPV, the risk of re-vaccination side effects is zero.** "Over 35 years of OPV use in the United States has resulted in no documented case of circulating vaccine-derived polioviruses (cVDPVs)," wrote Gallo and colleagues in *Science*. In contrast, up to 1% of BCG recipients require medical attention, due to adverse reactions.

Some scientists have also raised concerns that OPV and other live vaccines could **increase the risk of "cytokine storms"** that are deadly inflammatory reactions observed in some COVID-19 patients. Dr. Mihai Netea, an immunologist at Radboud University in the Netherlands, who is leading an OPV trial, does not anticipate problems, in part because the vaccines will only be given to healthy people, not patients already infected. BCG may also ramp up the body's initial immune response that reduces the amount of virus in the body, so an inflammatory response never occurs, notes a *New York Times* analysis.

Until an effective SARS-CoV-2 specific vaccine becomes widely available, nations may increasingly elect to repurpose existing live vaccines that could provide some protection. **If global clinical trials of BCG and OPV prove effective, major producers of those vaccines could benefit, including Sanofi** (SAN FP), **Merck** (MRK), **GlaxoSmithKline** (GSK LN), **and Takeda Pharmaceuticals** (4502 JP).

In *Science*, Gallo and colleagues summarize the equation:

> ***The strategy of inducing nonspecific protection may even have an advantage over a SARS-CoV-2-specific vaccine if SARS-CoV-2 undergoes mutation that leads to antigenic drift (and loss of vaccine efficacy), similar to seasonal influenza viruses.*** *If proven to be effective against COVID-19, emergency immunization with live attenuated vaccines could be used for protection against other unrelated emerging pathogens.*

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