

## A Call for a Three-Tiered Pandemic Public Health Strategy in Context of SARS-CoV-2

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**I**F LONGEVITY IS THE GOAL, then we must advocate for effective biodefense to deal with novel pandemics or face death from that quarter. For SARS-CoV-2, lack of early symptoms in all cases, and lack of any symptoms in approximately half, makes control of super-spreaders<sup>1</sup> by contact tracing and quarantine impractical. Thus, social distancing, masking, and mass lockdown was created to prevent overwhelming the medical system. That worked, but with economic impact that could kill millions or cast them into dire poverty.<sup>2,3</sup>

Economic disruption also spreads like a virus, but one that is impossible to “socially distance” from. Follow-on effects from the loss of income in these sectors will exacerbate these direct declines. In the developed world, after panic buying, people hoard money, causing the turnover of money to drop, thus reducing the effective money supply.<sup>4</sup> The lockdown dramatically cuts both demand and supply: the weekly increase in new unemployment claims for March 28, 2020 was 6.6 million, versus a recent average of 210,000.<sup>5</sup> This is eight times the largest percentage rate of increase in unemployment during the Great Depression. The World Trade Organization (WTO) estimates greater impact than the 2008 Global Financial Crisis,<sup>6</sup> and historically underestimates.

Conservative counting of industries directly affected—education, entertainment, accommodation, restaurants, real estate, and passenger transportation—represents 24% of U.S. GDP, almost equal to the total fall in GDP between late 1929 and 1933 (the bottom of the Great Depression) of 26%. Follow-on effects from the loss of income in these sectors will exacerbate these direct declines. A financial crisis will follow, since private debt to GDP levels is three times the level at the time of the Spanish flu.<sup>7</sup> Without strong government action, a financial pandemic will follow the medical pandemic.

Figure 1 shows the missing global economy from 2008's crisis is \$8.074 trillion for 2019. For the United States, relative losses averaging \$1.8 trillion per year comprise 12×\$1.8 trillion GDP years, or ~\$21.6 trillion cumulatively. This is what a 4.2% GDP maximum loss caused.

There is a general economic principle to keep in mind. Destruction is quick. Rebuilding is not.

It should be clear we need better methods than lockdown quarantine to combat pandemics such as SARS-CoV-2.

Fifteen years ago the first author was one of several to urge U.S. Congress to adopt a biodefense strategy<sup>8</sup> updated here as three tiers:

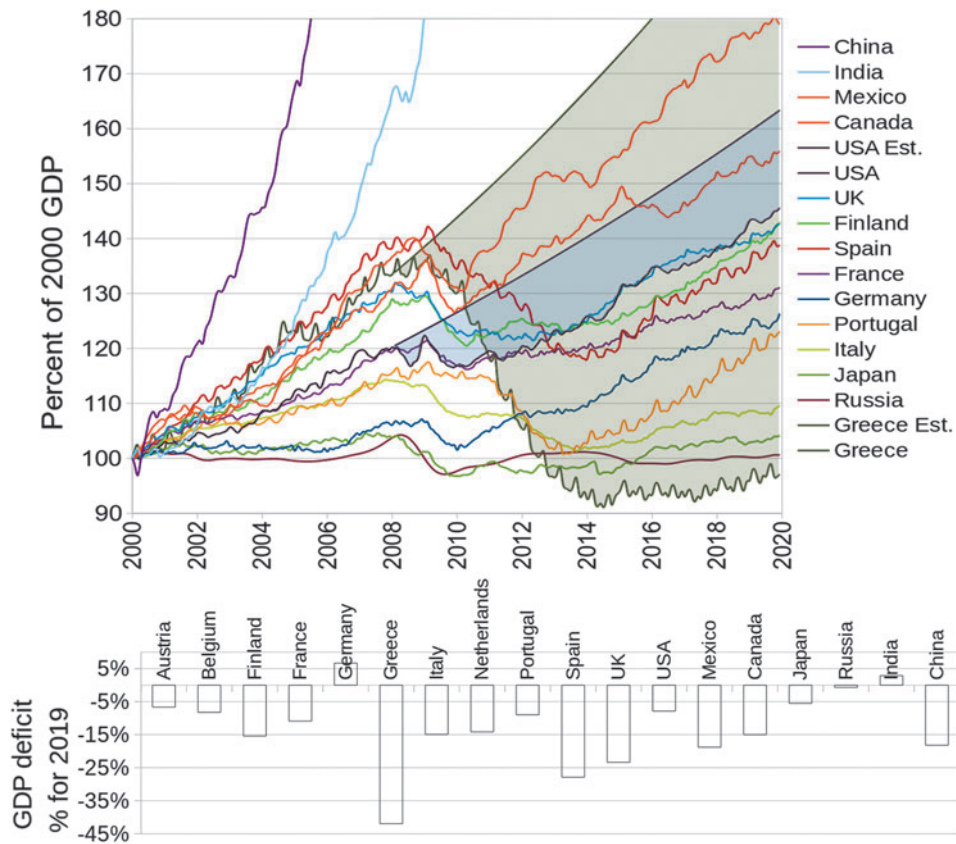
- (1) Recognize that medicine is biodefense. If a genuine bioweapon release occurs, it is virtually certain to be a nonstate actor, and that event could make SARS-CoV-2 a relative tea party. Mortality rates in the 60%–90% range are possible. This means that a national health care system is a fundamental security requirement so that nobody gets missed, because infectious diseases circulate well in poor and illegal populations.
- (2) We need to continuously monitor circulating viruses through excess blood/serum, and to inventory zoonotic viruses in wild animals. The former requires changing privacy laws in some nations to enable monitoring for public health purposes. Both require active prospecting for new microorganisms by sophisticated methods.
- (3) We need to set up and regularly exercise facilities for producing and deploying crisis vaccines rapidly in three waves: rolling out nucleotide vaccines expressing whole capsid/envelope proteins, then protein component/killed vaccine with adjuvant, followed by live attenuated/engineered vaccine. Each type has strengths. Nucleotide vaccine is quick to design and produce, safe for the immune compromised, and tends to avoid Th2 issues, but DNA is expensive to scale, whereas RNA is not. Component/killed vaccine often scales well and is also safe for the immune compromised. Live vaccine likewise scales well, although there are exceptions, and it usually produces the most robust immunity.

This vaccine strategy needs a special regulatory framework that eliminates roadblocks. Vaccines are very safe, and they work reliably on virtually all viruses when put together in straightforward ways. Rare exceptions like HIV are just that—incredibly rare exceptions. There are some risks, but reactions usually resolve.<sup>9</sup>

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**FIG. 1. Upper: GDP% loss by year.** Example projection estimates show where Greece and the United States should be relative to actual GDP. Respective 2019 GDP deficits: Greece 42.0% and United States 7.8%. Shading emphasizes deficit regions for Greece (brown) and United States (blue), showing time impact. Netherlands removed for readability. **Lower: 2019 GDP deficit due to 2008 crisis, based on 2000 starting point fit.** Total 2019 GDP deficit is \$8.074 trillion. WTO expects worse effect than 2008.<sup>4</sup> Source: BIS tables.<sup>12</sup> GDP, gross domestic product; WTO, World Trade Organization.

The smallpox vaccine had a 1 in 175 risk of myopericarditis.<sup>10</sup> The attenuated polio vaccine still has reversion. These vaccines are evaluated correctly based on relative risk, which includes mortality, morbidity, plus economic harm, and national security.

The purpose of a public health system vaccine crisis capability should be the immediate release and production of vaccines, in a wartime-like operation. Done this way, vaccines could be available weeks or a few months after the initial identification of the pathogen. Rollout becomes the trial, with monitoring evaluated strictly on risk versus benefit, that includes economic impact (which is the poverty and death impact of inaction versus action) as well as a casualty ratio.

Risk-benefit analysis in vaccines has examples that are far off base today. A respiratory syncytial virus vaccine in 1956 that caused some children <2 years to have risk of a worse respiratory illness. This vaccine was pulled, and yet it was fine for those >2 years.

RotaShield was a Wyeth vaccine in 2000 that had five cases of intussusception, causing it to be pulled. Intussusception is easily treated, and this was likely a fluke not related to the vaccine itself; but even if it was a rare side effect, the sensible thing to do was keep it until a replacement appeared. Rotavirus killed more than half a million children a year. From this decision, in the intervening years before a new vaccine ar-

rived, >4 million children had no chance of survival, including 320 in the United States and 1800 in Europe.

During the 2014 Ebola epidemic, several vaccines had been in development for a decade. Although two trials occurred, by withholding these vaccines instead of an immediate rollout, 28,852 people died and African nations incurred severe economic damage, including complete collapse of the Liberian medical system 6 months after the epidemic started. In 2018's Ebola outbreak, not until August was a vaccine introduced<sup>11</sup>; containment stopped it at 3000 odd deaths.

Foot dragging and wild misjudgment of vaccine risk are not acceptable. Likewise, withholding vaccines because of bureaucracy when a pandemic is raging. Since roadblocks are not just governmental, but also from corporate liability avoidance, legislation needs to include the ability for public health authorities to order production and release until something better is available, and to shield developers against liability.

Vaccines are the safest form of medicine we have, and the most cost-effective. For comparison, NSAIDS kill tens of thousands worldwide each year, and an estimated 7600 in the United States alone. Orthopedic surgery has an acute mortality rate of 1%. Total mortality from adverse reactions to vaccines in the past 50 years is very low, in the range of hundreds, and even these were mostly avoidable. Contamination and quality control are the major concerns in the

modern world. We are long past the ignorance that led to the reversion problems of the original Salk vaccine.

For this pandemic, open the gates and release the vaccines (#ReleaseTheVacc). Nucleotide vaccines are ready. They should have virtually zero safety issues. These will be protective against serious disease and prevent death in most cases, although not sterilizing. However, very few vaccines produce truly sterilizing immunity. The extremely rapid scaling of RNA vaccine makes it the superior method for mass deployment. RNA vaccines also have better antibody response than DNA vaccines.

Component and killed vaccines are also safe for immune compromised. Release them now as well.

Live recombinant and attenuated vaccines need the most testing, but even those can be moved through much faster. One can examine the design, looking at the base virus used and see safety of the scaffold in humans. Similarly, for attenuated vaccines, we can look at the gene(s) selected for removal/modification to attenuate the virus. Unlike Salk's era, we can do rational design because we understand the genes of viruses now.

Nothing is absolutely zero risk. But risk must be weighed against certainty of doing nothing, which here and now is too extreme.

We also recommend a backstop based on vaccinia (or some other suitable virus) for expression of novel virus proteins. Vaccinia can be quickly engineered to express virtually anything. As a live vaccine, in a dire emergency, such an engineered vaccine could be administered with directions to take a scraping from the sores that develop, and scratch it onto the shoulders of as many people who are not immune compromised as possible. This is the fastest possible rollout of a biodefense vaccine, although it comes with significant risk. The first author did scenarios for biodefense, and there are situations wherein this kind of rollout is the only plausible method to save a nation from collapse.

We call for all elements of this program to be legislated and supported by governments around the world. We suggest that it be supported by international treaty, with sanctions against nations that fail to comply. When nations are at risk of serious economic disruption or overwhelming health care facilities, there is no justification for current policies that leave no alternative but mass death and severe economic damage. It is worth remembering that the last global depression was ended by world war and a new world order.

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