A call for a three tiered pandemic public health strategy in context of SARS-CoV-2

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In context of the SARS-CoV-2 pandemic, articles such as Han, et al's current issue paper detailing epidemiology of acute respiratory illness are timely. This data is not easy to collect, and such studies can help inform our methods for mitigation and containment. Lloyd-Smith, et al's analysis of SARS-CoV-2003 epidemic data showed a huge variance in numbers one individual infects, and characterized "super-spreaders" as key [1], with infection contacts a quasi-scale-free network, as in metadata studies. Thus, ideally epidemic control identifies what potentially infectious contacts are, and focuses on identifying super-spreaders first. The SARS-CoV-2 pandemic's epicenter certainly appears to be an initiating super-spreading event. However, lack of early symptoms and lack of most symptoms in roughly half infected, make contact tracing and easy screening difficult.

Economic disruption also spreads like a virus, but one that is impossible to "socially distance" from. After panic buying, people hoard money, causing the turnover of money to drop, reducing the effective money supply by potentially 3 or 4 times [2]. The lockdown dramatically cuts both demand and supply: the weekly increase in new unemployment claims for March 28th, 2020 was 6.6 million, versus a recent average of 210,000 [3]. This is eight times the largest percentage rate of increase in unemployment during the Great Depression. The WTO estimates greater impact of lockdown than the 2008 GFC [4], and historically underestimates.

Conservative counting of industries directly affected—education, entertainment, accommodation, restaurants, real estate, and passenger transportation—represents 24% of US 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 are 3 times the level at the time of the Spanish Flu [5]. Without strong government action, a financial pandemic will follow the medical pandemic.

Figure 1 shows the economic losses from 2008. The missing economy due to 2008's crisis totals $8.074 trillion for 2019. These losses have been ongoing for 12 years and will continue forward.

It should be clear we need better methods than lockdown quarantine to combat pandemics like SARS-CoV-2. Even with quarantine methods, health care systems may be overwhelmed.

Fifteen years ago the first author was one of several to urge US Congress to adopt biodefense strategy [6] updated here as three tiers:

1. Recognize that medicine <u>is</u> biodefense. If a genuine bioweapon release occurs, it is virtually certain to be a non-state actor, and that event could make SARS-CoV-2 a relative tea party. 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 via 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. More than just ELISA tests, this requires 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 immuncompromised, and tends to avoid Th2 issues, but is expensive to scale. Component/killed vaccine scales better and is also safe for immunocompromised. Live vaccine gnerally scales well, and produces 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 some risks, but reactions usually resolve [7].

The smallpox vaccine that eradicated this disease had a 1 in 175 risk of myopericarditis [8]. The attenuated polio vaccine still has reversion. These vaccines are evaluated correctly based on relative risk, which includes mortality and 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 poverty and death impact) as well as a casualty ratio.

Risk/benefit analysis in vaccines has examples that are far off base today. An RSV vaccine in 1956 that caused some children under 2 to have risk of a worse respiratory illness. This vaccine was pulled, and yet it worked fine for those over 2.

RotaShield was a Wyeth vaccine in 2000 which had 5 cases of intussusception, which caused it to be pulled. Intussesception is easily treated, and this was likely a fluke and 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 over half a million children a year. In the intervening years before a new vaccine arrived, over 4 million children had no chance of survival by this decision, including 320 in the USA, and 1800 in Europe.

During the 2014 Ebola epidemic, several vaccines had been in development for a decade. While 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 [9]; containment stopped it at 3000 odd deaths.

Current foot dragging and miscalculation of vaccine risk is not acceptable. Likewise, withholding vaccines because of bureaucracy when a pandemic is raging is not acceptable. 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 (provided there is transparency).

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 USA alone. Orthopedic surgery has an acute mortality 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 of product are the the major concerns.

We recommend nucleotide vaccines roll out first, because they are fast, and done correctly, they should have virtually zero safety issues. Nucleotide vaccines that produce simple component protein should produce no Th2 response.

Live recombinant and attenuated vaccines need the most testing, but even those can be moved through more quickly. One can examine the design, looking at the scaffold virus used and see safety of the scaffold in primates, or humans. One can look at the gene(s) selected for removal/modification to attenuate the virus, then the expression of a novel protein on the scaffold's surface. We have learned enough now to do this. There is always risk, but that must be weighed against the impact of doing nothing. This type of vaccine is generally easiest to scale to hundreds of millions of doses.

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 immuno-compromised as possible. This is the fastest possible rollout of a biodefense vaccine, although it comes with some risk. The first author did scenarios for biodefense, and there are situations where this 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.

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Figure 1 Upper: GDP% loss by year. *Example projection estimates show where Greece and USA should be relative to actual GDP. Respective 2019 GDP deficits: Greece 42.0%, USA 7.8%. Shading emphasizes deficit regions for Greece (brown) and USA (blue), showing time impact. Netherlands removed for readability.*

Figure 1 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 impacts than 2008 [4].*

Source: BIS tables [10].

Footnote page

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