THE COVID-19 VACCINE DILEMMA

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ABSTRACT:

Covid-19 has led to large numbers of deaths, harms, and financial costs. Without an effective vaccine, those will continue. The pressure to find a vaccine is high; and that pressure creates a risk that the safeguards in place to assure that vaccines are safe and effective will be ignored. The U.S. has an extensive apparatus to oversee vaccine safety before and after licensing, including multiple federal committees and several monitoring systems, and that apparatus gave us, in 2020, an extraordinarily safe vaccine supply. This article explains the different pressures that push for and against using the same apparatus for Covid-19 vaccines, including the extensive harms from the disease on one side and the need for a vaccine that is, in fact, safe and effective from the other. It examines the options for speeding up the process without sacrificing too much oversight. It examines which "shortcuts" are reasonable, which may be challenging, and which are bad ideas. Finally, it addresses three messaging challenges - overselling, undersharing, and responding to misinformation - and suggests how to handle them.

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INTRODUCTION

On June 4, 2020, Science Magazine published an article saying that

> When the news broke yesterday that Operation Warp Speed had selected five experimental COVID-19 vaccines to fast-track through testing and, potentially, mass-scale production, it was news even to some top scientists involved with the White House–led program.[2]

The article explained that

> Warp Speed will give the chosen companies "access to additional government money, help in running clinical trials and financial and logistical support for a manufacturing base that is being built even before it is clear which if any of the vaccines in development will work."

This article captured the fears of many observers, concerned about politically-motivated cutting of corners in developing Covid-19 vaccines. While there are several good reasons to want a vaccine fast, there are real concerns about rushing a vaccine to market in the wrong way, and this article featured several of them. It suggested that the choices were made without input from experts or oversight bodies, that they were not based on scientifically sound criteria (and by implication, that choices were politicized[3]). It suggested a lack of transparency in the process. These things could and maybe should undermine confidence that we are developing an effective, safe vaccine. By undermining trust, it also set up a situation that could increase hesitance to use the vaccine even by people who are usually pro-vaccine. It was an example of speeding up done wrong. It doesn't have to be this way.

In less than six months COVID-19 has dramatically changed our world, globally and in the United States, killing over a hundred thousand Americans, hospitalizing many more, shutting down the economy, and leading most states to issue stay-at-home orders, at least for a time.[4] Citizens, experts, and policymakers struggle to deal with the disease. The long-term solution for the challenges from the disease poses, experts agree, is a vaccine that will allow people to develop immunity to the virus without having to be infected.[5]

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[2] Jon Cohen, *Top U.S. Scientists Left Out of White House Selection of COVID-19 Vaccine Short List*, SCIENCEMAG.ORG (June 4, 2020, 7:45 PM), https://www.sciencemag.org/news/2020/06/top-us-scientists-left-out-white-house-selection-covid-19-vaccine-shortlist/ (giving the name "Operation Warp Speed" to a government project aimed to speeding up vaccine development).

[3] *See* Ezekiel J. Emanuel & Paul A. Offit, *Could Trump Turn a Vaccine Into a Campaign Stunt?*, THE NEW YORK TIMES (June 8, 2020), https://www.nytimes.com/2020/06/08/opinion/trump-coronavirus-vaccine.html (concerning politicizing the process).

[4] *Maps & Trends: Mortality Analyses*, JOHNS HOPKINS UNIVERSITY & MEDICINE (last visited June 17, 2020), https://coronavirus.jhu.edu/data/mortality; Robert O. Bonow, et al., *Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality*, JAMA NETWORK (March 27, 2020), https://jamanetwork.com/journals/jamacardiology/article-abstract/2763844;
Martin Sparre Andersen, Ph.D. MPH, *Early evidence on social distancing in response to Covid-19 in the United States*, SSRN (April 6, 2020), https://ssrn.com/abstract=3569368.

[5] Stewart Lyman, *If Pharma Helps Quench the Covid-19 Pandemic, What Will it Want in Return?*, STAT NEWS (April 21, 2020), https://www.statnews.com/2020/04/21/vaccine-quenches-covid-19-what-will-pharma-want-in-

Generally, the vaccine development process takes many years. But waiting the usual years or decades will lead to many deaths and extensive harms.[6] The pressure to get a vaccine to market fast is immense because the costs of allowing COVID-19 to go unchecked are very high – but speeding up the process comes with real risks. The United States has a very robust system for testing vaccines and monitoring their safety. That system has resulted in an extraordinarily safe vaccine supply.[7] Some things can and likely should be done to speed it up; there are things that may be done that are more controversial – and there are things that likely should not be done. This article examines what can or should be done to speed up COVID-19 vaccine development, but also what shouldn't be.

Pressures may lead to errors and failures in three spheres: oversight failures, ethical failures, and messaging failures. The pressure could lead to unjustified corner-cutting in the testing process for the vaccine and pressures on oversight bodies to ignore problems even after the vaccine is licensed. Yet, in the pandemic context non-action also carries real costs, and in such times, there is no cost-free or risk-free choice. Both sides of this dilemma need to be considered when making choices.

Other concerns are about messaging failures, such as over-optimistic messaging promising more than reality supports, as well as messaging that creates concerns in the public that the vaccine produced will be unsafe – even when that's not the reality.

This article proceeds in four parts. Part I explains the regulatory framework governing vaccines licensing and monitoring in routine times. Part II explains the dilemma COVID-19 poses for vaccine development. Part III sets out possible scenarios, addressing regulatory concerns and ethical concerns. Part IV addresses potential messaging pitfalls and their harms. I then conclude.

PART I: REGULATORY FRAMEWORK

Vaccines are classified as biologics under the Public Health Service Act of 1944.[8] In practice, this means that vaccines are subject to both the requirements of the Public Health Service Act and to requirements the FDA applies to licensing drugs under the Food, Drug and Cosmetics

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return/; Lois Privor-Dumm, et al., *The Success of a Covid-19 Vaccine Will Hinge on its Delivery*, STAT NEWS (April 25, 2020), https://www.statnews.com/2020/04/25/success-covid-19-vaccine-hinge-on-delivery/.

[6] The usual process takes over a decade. Cecile Artaud, Leila Kara, and Odiel Launay *Vaccine Development: From Preclinical Studies to Phase 1/2 Clinical Trials*. 2013 Malaria Control and Elimination 165, 165-166 (2019). https://link.springer.com/protocol/10.1007/978-1-4939-9550-9_12

[7] *Ensuring Vaccine Safety*, CENTERS FOR DISEASE CONTROL AND PREVENTION (Sept. 29, 2015), https://www.cdc.gov/vaccinesafety/ensuringsafety/index.html. ("The United States has the safest, most effective vaccine supply in its history. The vaccine safety system ensures that vaccines are as safe as possible.")

[8] 42 U.S.C. §262(i) (2018). Biologics are defined as as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product or arsphenamine or derivative of arsphenamine" applicable to the prevention, treatment, or cure of a disease or condition of human beings. Kathleen R. Kelleher, *FDA Approval of Generic Biologics: Finding a Regulatory Pathway*, 14 MICH. TELECOMM. TECH. L. REV. 245, 246 (2007).

Act.[9] Marketing a biologic requires the sponsor, usually a pharmaceutical company, to submit a Biologics License Application,[10] which requires showing that the biologic is "safe, pure, potent and effective."[11] The FDA interprets the Public Health Safety Act to require that biologics – like other drugs – undergo "controlled clinical investigations" in humans.[12] To get to that stage – human clinical trials – the sponsor must submit an Investigational New Drug (IND) application to the FDA.[13] This requires that "preclinical studies should be sufficient to rule out overt toxicity and identify potential toxic effects that might occur during the clinical trial."[14] Once the IND has been submitted, the FDA has 30 days to object, or the clinical trial may proceed.

The IND application usually requires evidence of safety and immunogenicity (ability to elicit an immune response – that the vaccine candidate works) in animals, as well as other data.[15] The vaccine then undergoes three stages of clinical trials, described by the FDA thus:[16]

> Pre-marketing (pre-licensure) vaccine clinical trials are typically done in three phases, as is the case for any drug or biologic. Initial human studies, referred to as Phase 1, are safety and immunogenicity studies performed in a small number of closely monitored subjects. Phase 2 studies are dose-ranging studies and may enroll hundreds of subjects. Finally, Phase 3 trials typically enroll thousands of individuals and provide the critical documentation of effectiveness and important additional safety data required for licensing.

The completed trials are then submitted to the FDA's Center for Biologics Evaluation and Research (CBER), where a "multidisciplinary FDA reviewer team (medical officers, microbiologists, chemists, biostatisticians, etc.)" reviews the evidence.[17] If the team gives the go ahead, the material is submitted to the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC), which advises the FDA about the vaccine's safety and effectiveness.[18]

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[9] Edward L. Korwek, *Human Biological Drug Regulation: Past, Present, and Beyond the Year 2000,* 50 FOOD & DRUG L. J. 123, 129 (1995); Kathleen R. Kelleher, *FDA Approval of Generic Biologics: Finding a Regulatory Pathway*, 14 MICH. TELECOMM. TECH. L. REV. 245, 248 (2007).
[10] 42 U.S.C. §262(a)(1)(A) (2018).
[11] Tam Q. Dinh, *Potential Pathways for Abbreviated Approval of Generic Biologics under Existing Law and Proposed Reforms to the Law*, 62 FOOD & DRUG L.J. 77, 84 (2007).
[12] *Id.*; *see also The Journey of Your Child's Vaccine*, CENTERS FOR DISEASE CONTROL AND PREVENTION (June 30, 2018), https://www.cdc.gov/vaccines/parents/infographics/journey-of-child-vaccine-h.pdf
[13] 21 C.F.R. § 312.2(a) (2003).
[14] Valerie Marshall, Norman W. Baylor, *Food and Drug Administration Regulation and Evaluation of Vaccines*, 127 PEDIATRICS S23, S26 (2011).
[15] *Vaccine Product Approval Process.* U.S. FOOD & DRUG ADMINISTRATION (Jan. 30, 2018), *https*://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-product-approval-process.
[16] *Id*.
[17] *Id.*; s*ee also* Valerie Marshall, Norman W. Baylor, *Food and Drug Administration Regulation and Evaluation of Vaccines*, 127 PEDIATRICS S23, S27 (May 2011).
[18] *Id.*; *see also* Valerie Marshall, Norman W. Baylor, *Food and Drug Administration Regulation and Evaluation of Vaccines*, 127 PEDIATRICS S23, S27 (May 2011).

Since one of the things that separates licensing of biologics from licensing of drugs is that for biologics the manufacturing plant is also licensed, during the review period the manufacturing plant and process of producing the vaccine is also subject to inspection and review.[19]

Normally, this takes time.[20]

Table 1: Vaccine Development Timeline, an Estimate:[21]

Time Period	**Stage**	**Description**
Month 0-24 (This can also take many years).	**Preclinical**	Scientists attempt to identify a part of the virus which stimulates the immune memory so that the immune system can quickly destroy the pathogen before it can do harm. They also need to isolate and culture a substantial quantity of viruses that will be used in preclinical studies. These steps help scientists understand a virus's or bacterium's characteristics and pathophysiology in humans. Since it's unethical to do these studies in humans, researchers need to develop an animal model that mimics the response to the pathogen in a human. Also, researchers need to determine if the vaccine candidate is safe and triggers an adaptive immune response in that animal model.

[19] Valerie Marshall, Norman W. Baylor, *Food and Drug Administration Regulation and Evaluation of Vaccines*, 127 PEDIATRICS S23, S27 (May 2011).

[20] Ana Santos Rutschman, *The Vaccine Race in the 21st Century,* 61 ARIZ. L. REV. 729, 731 (2019) (The time this takes is an issue not only during pandemic time, but generally, meaning, as it does, that vaccines are not ready when the threat of a new pathogen is highest).

[21] *Coronavirus Vaccine Development – It's Going to Take a Long Time*, SKEPTICAL RAPTOR (April 19, 2020), https://www.skepticalraptor.com/skepticalraptorblog.php/coronavirus-vaccine-development-its-going-to-take-a-long-time/ (Note that this description assumes the virus or bacterial causing the disease has been identified – which is not obvious – and that the timeline is likely optimistic. For example, the rotavirus vaccine took 26 years to develop.); *Sabin Institute Honors Paul Offit, MD, Vaccine Champion*, CHILDREN'S HOSPITAL OF PHILADELPHIA (May 2, 2018), https://www.research.chop.edu/cornerstone-blog/sabin-institute-honors-paul-offit-md-vaccine-champion; Greg Johnson, *Q&A with Paul Offit*, PENNTODAY (May 14, 2015), https://penntoday.upenn.edu/2015-05-14/interviews/qa-paul-offit.

Month 24	**IND application**	The sponsoring organization (usually a pharmaceutical company) makes an Investigational New Drug (IND) application to the FDA's Center for Biologics Evaluation and Research CBER) to begin clinical trials. CBER reviews the IND and the sponsor can proceed with the clinical trial within 30 days if the FDA does not find cause to stop it from moving forward.

Month 24-60 (or more)	**Clinical trials**	The sponsoring organization must get Institutional Review Board (IRB) approval to proceed with human clinical trials. Clinical studies have three phases, although the process could be shortened if the data are very clear and there is a public need. Phase 1 clinical trials usually include a few tens of healthy patients (with no comorbidities and generally lack any chronic health conditions). This study is not usually randomized or blinded, as there is only one group, those that receive the vaccine. Phase 1 clinical trials are intended to alert you to safety problems or signals – and help determine vaccine dose. Many studies terminate after Phase I because of safety concerns. But at this point, you do not have good information about safety or effectiveness. Phase 2 clinical trials usually include around 200-300 patients. This study is a randomized, double-blind trial. It provides initial indications of effectiveness and safety, which help researchers determine if there is justification to move forward to the next phase. Phase 3 clinical trials, sometimes called pivotal studies, include around 2-3 thousand patients though for vaccines there could be tens of thousands of subjects. These studies are usually randomized, double-blinded, and placebo-controlled (or using a standard of care control). Phase 2 and 3 clinical trial results, when showing success, are often published in peer-reviewed journals.

Month 60-78	**Regulatory review and approval**	After all of the preclinical and clinical testing is completed, the sponsoring organization must submit a Biologics License Application (BLA) to CBER. At the same time, a manufacturing plan has to be developed. Vaccine manufacturing is complex and time-consuming. There might be enough excess capacity to make 200 million coronavirus vaccines across the world, but that's not much. New manufacturing facilities will need to be built to provide more capacity. Of course, these facilities also need to be reviewed and approved by regulatory authorities.

Vaccine development takes time for a number of reasons. The time may be needed to set up the clinical trials. Volunteers that fit the trial's requirements need to be recruited. Patients should represent broad income, ethnic, and other groups. Then, the sponsor has to find investigators, has to get IRB approval, has to get the vaccines and placebos to the sites, and more.

The data has to be analyzed in various ways to see if the vaccine is safe and effective. Normally it would be unethical to intentionally expose the patients (both vaccinated and placebo groups) to the virus, so investigators need to wait for natural exposure. Without exposure, researchers cannot directly examine whether the vaccine works, and need to use imperfect surrogates (like antibody levels). As will be discussed below, one of the approaches considered to expedite COVID-19 vaccines is to intentionally expose volunteers to the virus. Further, to see whether immunity is more than transient, the trial will have to proceed for at least some months.

To give some examples, Gardasil – a vaccine against the Human Papilloma Virus – involved phase III trials that followed participants for about three years.[22] For rotavirus, infants were followed for a year.[23]

Other problems can slow down the process. Sometimes vaccines need to be reworked. When things do not work, scientists need to go back to the beginning and find a solution, if possible.

It's also important to remember that there is no guarantee any vaccine candidate will pass clinical trials. Clinical trials fail the vast majority of the time.[24] In the case of coronavirus vaccines, there are over one hundred vaccines in development, though only about a dozen have started clinical trials in humans.[25] We can hope that at least one of those candidates pans out, at least to some degree. But we cannot assume it.

Licensing is not the end of the process or of scrutiny. First, production is subject to continuing scrutiny - the FDA is expected to exercise some oversight over lots, or batches, of vaccines.[26] Historical experience supports this requirement: one of the worst vaccine disasters in the United States was the result of a mishandled manufacturing process. In the Cutter incident, over 200 children were paralyzed and 10 killed because a polio vaccine that should have contained an inactivated virus instead included a live, virulent virus. [27] Close oversight of the manufacturing process can help prevent similar tragedies. Another concern is the potential contamination of vaccines, and there have been several instances of contamination in the past.[28] Each lot of the licensed vaccine is subject to testing.[29] Licensed facilities need to be inspected at least every two years.[30]

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[22] Suzanne M. Garland, et al., *Quadrivalent Vaccine Against Human Papillomavirus to Prevent Anogenital Diseases*, 356 NEW ENG. J. MEDICINE 1928 (2007); Future II Study Group, *Quadrivalent Vaccine Against Human Papillomavirus to Prevent Anogenital Diseases*, 356 NEW ENG. J. MEDICINE 1915 (2007).
[23]Timo Vesikari, et al., *Safety and Efficacy of a Pentavalent Human–Bovine (WC3) Reassortant Rotavirus Vaccine*, 354 NEW ENG. J. MEDICINE 23 (2006).
[24] J.A. DiMasi, et al., *Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs*, CLINICAL PHARMACOLOGY & THERAPEUTICS (2010), https://pubmed.ncbi.nlm.nih.gov/20130567/ (success rate in clinical trials in the United States was 16% between 1999-2004).
[25] Ewen Callaway, *The Race for Coronavirus Vaccines: A Graphical Guide*, NATURE (April 28, 2020), https://www.nature.com/articles/d41586-020-01221-y (see appendix A for the vaccines currently in clinical trials).
[26] *Vaccine Product Approval Process.* U.S. Food & Drug Administration (Jan. 30, 2018), https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-product-approval-process; Tam Q. Dinh, *Potential Pathways for Abbreviated Approval of Generic Biologics under Existing Law and Proposed Reforms to the Law*, 62 FOOD & DRUG L. J. 77, 84 (2007).
[27] Paul A. Offit, *The Cutter Incident, 50 Years Later*, 352 NEW ENG. J. MEDICINE 1411 (2005); Brit Trogen, et al., *Adverse Consequences of Rushing a SARS-CoV-2 Vaccine*, JAMA NETWORK (May 26, 2020), https://jamanetwork.com/journals/jama/fullarticle/2766651.
[28] John Petricciani, et al., *Adventitious Agents in Viral Vaccines: Lessons Learned from 4 Case Studies*, 42 BIOLOGICALS 223 (2014).
[29] Valerie Marshall, Norman W. Baylor, *Food and Drug Administration Regulation and Evaluation of Vaccines*, 127 PEDIATRICS S23, S28-29 (2011); Theresa M. Finn, *U.S. FDA Requirements for Human Vaccine Product Safety and Potency Testing*, 5 PROCEDIA IN VACCINOLOGY 137, 139 (2011).
[30] Valerie Marshall, Norman W. Baylor, *Food and Drug Administration Regulation and Evaluation of Vaccines*, 127 PEDIATRICS S23, S29 (2011).

In addition, multiple oversight mechanisms exist to oversee vaccine safety after licensing (like VRBPAC does before licensing). This is not only to discover issues that may have been missed during trials but to discover issues trials are too small to discover. Clinical trials include up to tens of thousands of people, but they would not identify a problem that is as rare as, say, one per a hundred thousand. But continuing monitoring can find these rare problems. In the United States, the Department of Health and Human Services uses a combination of methods to monitor vaccine safety. These include oversight by federal expert committees as well as sophisticated databases to discover problems and analyses by researchers of those databases.

First, the Advisory Committee on Immunization Practices (ACIP), made up of 15 experts in "infectious diseases, pediatrics, internal medicine, family medicine, virology, immunology, public health, preventive medicine, vaccine research and policy, economics and cost-effectiveness" as well as a consumer representative, monitors vaccines, usually starting about two years before licensure.[31] ACIP makes recommendations about the vaccine schedule for children and adults and reviews vaccine safety data both during its meetings, which take place three times a year, and continuously through its workgroups.[32] For COVID-19 vaccines, a workgroup was created in April 2020.[33]

Also meeting three times a year is the National Vaccine Advisory Committee, whose duties include to "Study and recommend ways to encourage the availability of an adequate supply of safe and effective vaccination products in the United States," and to "Recommend research priorities and other measures the Director of the [National Vaccine Program, an office in the Department of Health and Human Services] should take to enhance the safety and efficacy of vaccines."[34] This committee includes fifteen public members, "selected from individuals who are engaged in vaccine research or the manufacture of vaccines, or who are physicians, members of parent organizations concerned with immunizations, representatives of State or local health agencies or public health organizations," and two representatives of the vaccine industry.[35]

Finally, among the responsibilities of the Advisory Committee on Childhood Vaccines are the duties to "advise the Secretary… regarding the need for childhood vaccination products that result in fewer or no significant adverse reactions." The Committee also has responsibilities in collecting data on vaccines' adverse reactions and suggesting research related to it.[36] This committee's members are "three … health professionals" with "expertise in the health care of children, the

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[31] *See* Jean Clare Smith, *The Structure, Role, and Procedures of the U.S. Advisory Committee on Immunization Practices (ACIP)*, 285 VACCINE A68 (2010).

[32] *See* Jean Clare Smith, *The Structure, Role, and Procedures of the U.S. Advisory Committee on Immunization Practices (ACIP)*, 285 VACCINE A68, A73-74 (2010); *see generally Advisory Committee on Immunization Practices (ACIP)*, CENTERS FOR DISEASE CONTROL AND PREVENTION (last updated Oct. 23, 2018), https://www.cdc.gov/vaccines/acip/committee/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Facip%2Fabout.html.

[33] This information draws on presentations at the June 24, 2020 virtual meeting of the Advisory Committee of Immunization Practices, which Dorit Reiss followed. The slides showing this will be posted online a few weeks after the meeting. A screenshot of the relevant slide is with the authors.

[34] *National Vaccine Advisory Committee Charter*, DEPARTMENT OF HEALTH & HUMAN SERVICES (last visited June 18, 2020), https://www.hhs.gov/vaccines/nvac/charter/index.html.

[35] *Id.*

[36] *Advisory Commission on Childhood Vaccines Charter*, DEPARTMENT OF HEALTH & HUMAN SERVICES, https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/vaccines/accvcharter.pdf; *see also* Efthimios Parasidis, *Recalibrating Vaccination Laws*, 97 B.U.L. REV. 2153, 2227 (2017) (suggesting the Committee should be used more).

epidemiology, etiology, and prevention of childhood diseases, and the adverse reactions associated with vaccines, of whom at least two shall be pediatricians," "three members from the general public", at least two "legal representatives of children who have suffered a vaccine-related injury or death," and "three… attorneys," at least one specializing in representing vaccine injury cases, and one who represents vaccine manufacturers.[37]

In addition to these advisory committees, populated by people with various relevant expertise, most from outside the government and several with strong interests in vaccine safety, there are four large computerized systems that collect data on vaccine risks.[38] These include the Vaccine Adverse Events Reporting System, a passive reporting system that anyone can report to, designed to provide early warnings of issues.[39] Although, as a passive monitoring system, VAERS has real limits, it has successfully in the past caught, for example, a rare (1:10,000) serious side effect of the first Rotavirus vaccine to be licensed in the United States, which was confirmed in an independent investigation.[40]

The other three monitoring systems are active monitoring systems. The Vaccine Safety Datalink, a collaboration between CDC and healthcare organizations covering millions of people, which includes both constant active monitoring of signals (by comparing on an ongoing basis people who received a vaccine and those who have not) and allows researchers to do in-depth analyses of specific issues.[41] Many studies are done using VSD data, and in 2018 a whitepaper on the safety of the entire schedule drew on it.[42]

The Post-Licensure Rapid Immunization Safety Monitoring System (PRISM), another large active system, is part of the FDA Sentinel System, a system designed to monitor medical products by tracking health insurance claims.[43] PRISM covers one hundred and ninety million people, allowing for studies larger than other systems.[44]

Finally, the Clinical Immunization Safety Assessment Project (CISA) allows providers to submit queries and get an expert evaluation about specific patients, including evaluations of whether a

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[37] *Id*.
[38] *See generally Vaccine Safety*, VACCINES.GOV (Feb. 2020), https://www.vaccines.gov/basics/safety.
[39] *Vaccine Adverse Event Reporting System (VAERS),* CENTERS FOR DISEASE CONTROL AND PREVENTION (Jan. 27, 2017), https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/.
[40] Jason Schwartz, *The First Rotavirus Vaccine and the Politics of Acceptable Risk,* 90 Milbank Q. 278, 285-289 (2012) (although Prof. Schwartz' account is cautionary, it highlights that the problems with the vaccine were raised – and followed on – within a few months of its use).
[41] *Vaccine Safety Datalink (VSD)*, CENTERS FOR DISEASE CONTROL AND PREVENTION (June 17, 2019), https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/.
[42] National Center for Emerging and Zoonotic Infectious Diseases. "White Paper Studying the Safety of the Childhood Immunization Schedule for the Vaccine Safety Datalink." U.S. Centers for Disease Control and Prevention. Accessed 5 July 2018. https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf.
[43] *See Vaccine Safety*, VACCINES.GOV (Feb. 2020), https://www.vaccines.gov/basics/safety; *see also Assessments*, SENTINEL (last visited June 18, 2020), https://www.sentinelinitiative.org/vaccines-blood-biologics/assessments/.
[44] Centers for Disease Control and Prevention. "Ensuring the Safety of Vaccines in the United States." Accessed 27 July 2018. https://www.cdc.gov/vaccines/hcp/conversations/downloads/vacsafe-ensuring-color-office.pdf. Shoaibi, Azadeh. "PRISM Identifies Vaccine Safety Issues." *FDA Voice*. 7 April 2017. Accessed 5 July 2018. https://blogs.fda.gov/fdavoice/index.php/2017/04/prism-identifies-vaccine-safety-issues/.

problem is vaccine-related or whether an existing condition is a contraindication to a vaccine.[45] CISA also conducts direct research on vaccine safety for specific issues and special populations.[46]

Besides these mechanisms in HHS, research is conducted in other parts of the United States government:

> "The Department of Defense (DoD) and U.S. Department of Veterans Affairs (VA) have systems to monitor vaccine safety and do vaccine safety research. The National Institutes of Health (NIH) and the Office of Infectious Disease and HIV/AIDS Policy (OIDP) also support ongoing research on vaccines and vaccine safety."[47]

In other words, extensive institutional arrangements for monitoring vaccine safety exist in the United States in relation to routine vaccines. These arrangements have resulted in a very high level of safety.[48] Summarizing that data, the National Academies of Sciences, Engineering and Medicine, in a special page linking to several of its extensive reports on the topic, concluded that "Vaccines are extremely safe. They have many health benefits and few side effects."[49]

PART II: COVID-19 AND THE CHALLENGE TO VACCINES

Normally, vaccine development takes years. But between February 2020 and May 2020, hundreds of thousands of people worldwide died from COVID-19.[50] By June 15, 2020 deaths in the United States topped 115,000.[51] And by many indications, this is an undercount of deaths.[52]

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[45] *Clinical Immunization Safety Assessment (CISA) Project*, CENTERS FOR DISEASE CONTROL AND PREVENTION (Jan. 29, 2020), https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html.
[46] Id.
[47] *Vaccine Safety*, VACCINES.GOV (Feb. 2020), https://www.vaccines.gov/basics/safety.
[48] Sarah Geoghegan, et al., *Vaccine Safety: Myths and Misinformation*, FRONTIERS IN MICROBIOLOGY (March 17, 2020), https://www.frontiersin.org/articles/10.3389/fmicb.2020.00372/full; Frank DeStefano, et al., *Principal Controversies in Vaccine Safety in the United States*, 69 CLINICAL INFECTIOUS DISEASES 726 (2019); *but see* Efthimios Parasidis, *Recalibrating Vaccination Laws*, 97 B.U.L. REV. 2153 (2017) (downplaying, for example, the role of the active monitoring systems described above, 2223-2225, and only briefly mentions one of the four advisory committees described here, 2210, 2217 in footnotes, 2227 in text).
[49] *Vaccines are Safe*, THE NATIONAL ACADEMIES OF SCIENCES (last visited June 19, 2020), https://sites.nationalacademies.org/BasedOnScience/vaccines-are-safe/index.htm; *See* Andre et al., *Ten Threats to Global Health in 2019*, WORLD HEALTH ORGANIZATION (last visited June 19, 2020), https://www.who.int/emergencies/ten-threats-to-global-health-in-2019. ("independent experts and WHO have shown that vaccines are far safer than therapeutic medicines. Modern research has spurred the development of less reactogenic products, such as acellular pertussis vaccines and rabies vaccines produced in cell culture. Today, vaccines have an excellent safety record and most "vaccine scares" have been shown to be false alarms.")
[50] *Coronavirus Disease (Covid-19) Situation Report – 127*, WORLD HEALTH ORGANIZATION (May 26, 2020, 10:00 AM), https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200526-covid-19-sitrep-127.pdf?sfvrsn=7b6655ab_8.
[51] *Coronavirus Disease 2019 (COVID-19) Cases in the U.S.*, CENTERS FOR DISEASE CONTROL AND PREVENTION (last visited June 19, 2019), https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html; *Coronavirus Resource Center*, JOHNS HOPKINS UNIVERSITY & MEDICINE (last visited June 19, 2020), https://coronavirus.jhu.edu/us-map.
[52] Stephanie Pappas, *How COVID-19 Deaths are Counted,* SCIENTIFIC AMERICAN (May 19, 2020), https://www.scientificamerican.com/article/how-covid-19-deaths-are-counted1/.

The virus has caused millions of cases of the disease.[53] The economic costs – both direct and indirect – are extensive, too. Looking at the United States alone, as of the week ending May 9, over 25 million people have applied for unemployment insurance.[54] Many small businesses are at direct risk of closing.[55] And the costs are not evenly distributed, exacerbating existing inequalities.[56] The harms, too, disproportionally (though not exclusively) fall on minority groups.[57] The economic impacts are not limited to the United States economy – many countries are struggling.[58]

Both the virus directly and the economic impacts pose real risks to people's health and lives.[59] Losing jobs can mean people who are already living on the margins of poverty may not be able to cover all their basic needs.[60] Some may face the loss of their home, and homelessness – or poverty generally – worsens health outcomes.[61] Not taking measures to contain spread would not necessarily spare the economy: people would respond to an uncontrolled pandemic by taking actions that would harm the economy.[62]

The high costs of the pandemic and its containment measures in lives, health and economic harms put pressure on policymakers and scientists to find a quick solution.[63] The long-term solution, experts agree, is having a safe, effective vaccine that will, ideally, prevent COVID-19 from infecting people and spreading in the population. Going through the regular process means

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[53] *Coronavirus Disease (Covid-19) Situation Report – 127*, WORLD HEALTH ORGANIZATION, (May 26, 2020, 10:00 AM), https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200526-covid-19-sitrep-127.pdf?sfvrsn=7b6655ab_8.

[54] *See*, *News Release, COVID-19 Impact*, U.S. DEPARTMENT OF LABOR (May 14, 2020), https://www.dol.gov/sites/dolgov/files/OPA/newsreleases/ui-claims/20200976.pdf.

[55] Michael Powe & Matthew Wagner, *The Impact of Covid-19 on Small Businesses*, NATIONAL MAIN STREET CENTER, https://higherlogicdownload.s3.amazonaws.com/NMSC/390e0055-2395-4d3b-af60-81b53974430d/UploadedImages/Resource_Center/COVID_19/NMSC57_MSA_COVID19IMAPCTSURVEY_F.pdf.

[56] Emily A. Benfer & Lindsay F. Wiley, *Health Justice Strategies to Combat COVID-19: Protecting Vulnerabile Communities During a Pandemic,* HEALTHAFFAIRS (March 19, 2020), https://www.healthaffairs.org/do/10.1377/hblog20200319.757883/full/

[57] Monica Webb Hooper, et al., *COVID-19 and Racial/Ethnic Disparities*, JAMA NETWORK (May 11, 2020), https://jamanetwork.com/journals/jama/article-abstract/2766098; Cato T. Laurencin, Aneesah McClinton, *The COVID-19 Pandemic: a Call to Action to Identify and Address Racial and Ethnic Disparities*, J. OF RACIAL AND ETHNIC DISPARITIES 398 (2020).

[58] Peterson K. Ozili, Thankom Arun, *Spillover of COVID-19: Impact on the Global Economy*, SSRN (Mar. 30, 2020), https://ssrn.com/abstract=3562570; *COVID-19's Historic Economic Impact, In the U.S. and Abroad,* JOHNS HOPKINS UNIVERSITY HUB (April 16, 2020), https://hub.jhu.edu/2020/04/16/coronavirus-impact-on-european-american-economies/.

[59] Martin McKee, David Stuckler, *If the World Fails to Protect the Economy, COVID-19 Will Damage Health Not Just Now But Also in the Future*, 26 NATURE MEDICINE 640 (2020).

[60] Emily A. Benfer & Lindsay F. Wiley, *Health Justice Strategies to Combat COVID-19: Protecting Vulnerabile Communities During a Pandemic,* HEALTHAFFAIRS (March 19, 2020), https://www.healthaffairs.org/do/10.1377/hblog20200319.757883/full/

[61] *Id*.

[62] Sergio Correia, et al., *Pandemics Depress the Economy, Public Health Interventions Do Not: Evidence from the 1918 Flu*, SSRN (Mar. 26, 2020), https://ssrn.com/abstract=3561560 PIERRE-OLIVIER GOURINCHAS, MITIGATING THE COVID ECONOMIC CRISIS: ACT FAST AND DO WHATEVER IT TAKES 35, 38 (Richard Baldwin & Beatrice Weder di Mauro eds., 2020), http://viet-studies.net/kinhte/COVIDEconomicCrisis.pdf#page=38.

[63] Stanley A. Plotkin & Arthur Caplan, *Extraordinary Diseases Require Extraordinary Solutions*, 38 VACCINE 3987 (2020).

a long wait for the vaccine. Understandably, policymakers – and citizens – are concerned about that. Policymakers correctly point out that while a vaccine rushed through the process can have risks, so can waiting until the usual testing is completed. Letting COVID-19 rage unchecked can kill many, and cause additional harms through economic consequences.[64]

On the other hand are the costs of having an unsafe vaccine. First, an unsafe vaccine can directly harm people – during previous vaccine scandals, like the Cutter Incident or the 1976 swine flu episode, people died or were paralyzed by a vaccine.[65] There is also some risk that a COVID-19 vaccine could predispose recipients to a more severe case of the disease.[66] Dr. Douglas Green explained:

> In 1966, a large trial of a vaccine for Respiratory Syncytial Virus (RSV) found that the immunized cohort actually faired [sic] significantly worse upon infection. There is some reason to worry that the same may occur with some SARS-CoV2 vaccines.
>
> …
>
> There are potential reasons why an immune response to a vaccine can predispose an individual to a worse outcome upon infection. One is the phenomenon of antibody-dependent enhancement (ADE). In this effect, antibodies that bind to the virus also bind to antibody receptors on cells, facilitating uptake and infection of the cell bearing the receptors. ADE has been observed for vaccines against Dengue, Ebola, and HIV. As recently as 2017, a large-scale efficacy trial of a Dengue vaccine resulted in ADE in vaccinated children. Troublingly, ADE has also been seen with vaccines for a feline coronavirus. There is also evidence for ADE in SARS-CoV. Studies have shown that rodent and human antibodies to the S protein can enhance infection in vitro. However, several small preclinical studies of a SARS-CoV vaccine in rhesus monkeys failed to observe evidence of ADE.
>
> One SARS-CoV2 vaccine, employing inactivated virus, was tested in several large cohorts of rhesus monkeys, with substantial efficacy and no evidence of ADE. While this is clearly encouraging, the need to ensure that any vaccine is, indeed, safe is of vital importance. [footnotes omitted][67]

Testing has to assure that a vaccine is not worse than the disease, and does not predispose the recipient to worse cases going forward.

But that comparison is not as straightforward as it seems. Every vaccine is approved on a risk/benefit basis: are the risks greater than the benefits? Every vaccine carries at least a

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[64] *Id*.
[65] Brit Trogen, et al., *Adverse Consequences of Rushing a SARS-CoV-2 Vaccine*, JAMA NETWORK (May 26, 2020), https://jamanetwork.com/journals/jama/fullarticle/2766651.
[66] Douglas R. Green, *SARS-CoV2 Vaccines: Slow is Fast*, SCIENCE ADVANCES (May 22, 2020), https://advances.sciencemag.org/content/early/2020/05/22/Sciadv.abc7428.full.
[67] *Id*.

theoretical risk of a severe allergic reaction, which if untreated can be fatal, though that risk is extremely small – around one per million overall, and for some vaccines purely theoretical.[68] Between 1961 and 1997 (and a few years afterward, since the process of transition was gradual) the polio vaccine used in the United States was the oral polio vaccine (OPV).[69] OPV causes paralysis in recipients in about one in 2.4 million doses.[70] But the benefits of the vaccine were considered high enough to justify the risk. For a COVID-19 vaccine, too, the question is not whether it will have any rare hidden risk, but whether the potential of rare hidden risks is higher than the risks of not giving the vaccine. That depends on several factors. During the pandemic, when cases are high and the effects of the pandemic severe and visible, we may be willing to tolerate a higher risk than when the disease declines.[71]

But this, too, needs to be examined more closely. First, the risks of the vaccine may not be equally distributed with the risks of the disease. For example, the risks of COVID-19, though they exist in every age group, vary – the risk of direct death or severe outcomes increases with age.[72] At the same time, there is growing evidence of a special inflammatory syndrome in children caused by COVID-19.[73] The highest risks of a new vaccine, however, may end up being in a group for whom the risks of COVID-19 are low. Is it ethical to impose a created risk on one group to protect another? Incomplete testing means we may not know who bears the risk, or the nature and severity of uncommon risks.

Further, the risks of vaccines are not treated as equivalent to the risks of the disease. As mentioned above, in 1998, a rotavirus vaccine with a 1:10,000 risk of a severe side effect was taken off the market because that risk was deemed too high to be acceptable in a vaccine – even though the risks of the disease were higher than 1:10,000 severe harm.[74] Giving a vaccine to a healthy person is not the same as treating someone who is sick, and just "risks higher than benefits" is not the standard actually used. Especially given what we have come to expect from modern routine childhood vaccines, whose risks are, in fact, extremely low, our safety expectations from vaccines are high.

We have already seen several examples in the context of the COVID-19 pandemic where rush led, potentially, to harm. For example, after the drug hydroxychloroquine (HCQ) was touted as a cure for COVID-19, FDA authorized its use – even though there was no good evidence to do

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[68] Michael M. McNeil, et al., *Risk of Anaphylaxis After Vaccination in Children and Adults*, 137 J. OF ALLERGY AND CLINICAL IMMUNOLOGY 868 (2016).

[69] *Poliomyelitis Prevention in the United States: Introduction of A Sequential Vaccination Schedule of Inactivated Poliovirus Vaccine Followed by Oral Poliovirus Vaccine; Recommendations of the Advisory Committee on Immunization Practices (ACIP)*, CENTERS FOR DISEASE CONTROL AND PREVENTION (Jan. 24, 1997), https://www.cdc.gov/mmwr/preview/mmwrhtml/00046568.htm

[70] *Id*.

[71] Frank Destefano, et al., *Vaccine Safety*, PLOTKIN'S VACCINES 1584, 1596 (2017).

[72] Dale Fisher & David Heymann, *Q&A: The Novel Coronavirus Outbreak Causing Covid-19*, 18 BMC MEDICINE, 57 (2020).

[73] Jennifer Couzin-Frankel, *Doctors Race to understand Rare Inflammatory Condition Associated with Cornavirus in Young People*, SCIENCEMAG.ORG (May 21, 2020), https://www.sciencemag.org/news/2020/05/doctors-race-understand-rare-inflammatory-condition-associated-coronavirus-young-people; Crystal Phend, *Targeting Immune Responses in Kids' COVID-19 Inflammatory Disorder*, MEDPAGE TODAY (May 21, 2020), https://www.medpagetoday.com/infectiousdisease/covid19/86614.

[74] *Withdrawal of Rotavirus Vaccine Recommendation*, CENTERS FOR DISEASE CONTROL AND PREVENTION (Nov. 5, 1999), https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4843a5.htm.

so.[75] Increasing amounts of data suggesting no benefit from using hydroxychloroquine to treat COVID-19 led to the FDA pulling the authorization.[76] The initial recommendation, in the meantime, was not harmless. The treatment in question had risks - and touting it as a cure for Covid-19 creates a risk that it will not be available for those who need it for diseases it has been shown to help with.[77] The risk of panic prescribing as a response to the pandemic is a real one, and the risk of panic approval of vaccines, with negative results, is one, too.[78]

Not only can an unsafe vaccine create harms that are ethically – and publicly – unacceptable, the resulting lack of trust may spill over to other vaccines and lead to lower vaccination rates – and attendant risks of outbreaks – for other diseases.[79] It could also negatively affect the willingness to comply with other public health recommendations – something dependent on trust.

PART III: OUR OPTIONS:

There are multiple ways to increase the speed of vaccine development. None is perfect or problem-free, but some are reasonable, some ethically challenging, and some outright dangerous. Note that dangers can come in two varieties: some approaches increase the risk of ending with an unsafe or ineffective vaccine, leading to a result that does not improve the pandemic situation. Others do not risk the final result, but can dramatically increase the risks to trial participants. One caveat: this section focuses on the process before licensing. We see no reason to relax the oversight and requirements in place after a vaccine is licensed, and indeed, one thing we think is particularly important is to preserve the oversight by respecting the role of advisory committees in the process and assuring transparency towards them. Oversight mechanisms after licensing should carefully monitor any licensed Covid-19 vaccines.

A straightforward approach that has been used before is to do multiple testing phrases together. For example, several companies are conducting phase 1 and phase 2 trials simultaneously.[80] Overlapping trial stages are not unusual, and there may be good reasons to go back and forth – for example, there may be something that needs testing in a smaller, more intensive trial while a

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[75] Jinoos Yazdany, Alfred H.J. Kim, *Use of Hydroxychloroquine and Chloroquine During the COVID-19 Pandemic: What Every Clinician Should Know*, ANNALS OF INTERNAL MEDICINE (June 2, 2020), https://www.acpjournals.org/doi/full/10.7326/M20-1334.

[76] Letter from Dinese M. Hinton, Chief Scientist, Food and Drug Administration, to Gary L. Disbrow, Director, Biomedical Advanced Research and Development Authority, U.S. Department of Health and Human Services (June 15, 2020), https://www.fda.gov/media/138945/download; Joe Palca, *FDA Withdraws Emergency Use Authorization For Hydroxychloroquine*, NPR (June 15, 2020), https://www.npr.org/sections/coronavirus-live-updates/2020/06/15/877498151/fda-withdraws-emergency-use-authorization-for-hydroxychloroquine.

[77] Camela Thompson, *Life with Lupus: Trump's Hydroxychloroquine Hype Puts my Treatment — and Himself — at Risk*, STAT NEWS (May 20, 2020), https://www.statnews.com/2020/05/20/hydroxychloroquine-trump-hype-jeopardize-supply-may-harm-him/.

[78] Holly Fernandez Lynch, et al., *'Panic Prescribing' Untested Coronavirus Treatments: A Danger To Patients Today and Tomorrow*, HEALTHAFFAIRS (March 31, 2020), https://www.healthaffairs.org/do/10.1377/hblog20200330.265604/full/.

[79] Brit Trogen, et al., *Adverse Consequences of Rushing a SARS-CoV-2 Vaccine*, JAMA NETWORK (May 26, 2020), https://jamanetwork.com/journals/jama/fullarticle/2766651.

[80] *Coronavirus Vaccine Trials – Updating Current Studies Across the World*, SKEPTICAL RAPTOR (June 9, 2020), https://www.skepticalraptor.com/skepticalraptorblog.php/coronavirus-vaccine-trials-updating-current-studies-across-world/.

large trial is going on. In addition, as mentioned previously, phase 1 trials do not typically provide a lot of information about the vaccine, so combining them with phase 2 trials may speed up the development process.

Another time-saving approach is to prepare large trials early. For example,

> Under a proposal under discussion by a committee set up by the National Institutes of Health, each of four or five experimental vaccines would be tested on about 20,000 trial participants with a placebo group of 10,000 for each vaccine. Some 50 U.S. medical centers — and perhaps an equal number overseas — would participate in these trials.[81]

Setting up these large trials now could save time later, and is a reasonable, likely uncontroversial step. It has financial risks. But it will not undermine vaccine safety or effectiveness. As further suggested in an editorial, these could be done as "adaptive randomized-controlled" trials:

> These trials can be structured to evaluate multiple vaccine candidates against a common control group and can shift enrollment based on which vaccines are most promising. Vaccines would be selected based on their promise in early studies and how quickly their manufacturing can be scaled. With so many patients developing mild or no symptoms, clinical trials will need to be large. But this is the best shot at quickly identifying safe and effective vaccines.[82]

These trials are costly. And if government-run, costs that usually fall on companies – costs of testing vaccines that may well never make it to market – will fall on the taxpayers. But in the context of a harmful, disruptive pandemic, that may be justified. That said, these trials need to be focused on the best vaccine candidates from a scientific perspective. Political selection of the candidates to be supported by the government – or those receiving production support – undermines legitimacy and can directly counter the search for a better vaccine.[83]

Also costly, but not controversial from the point of view of safety, is setting up production before trials are complete – something suggested both in the United Kingdom and in the United States.[84] These approaches too carry an economic risk: preparing for production is costly, and if the vaccine candidate in question does not succeed in a clinical trial, the investment would have been for nothing. The investment itself does not, however, create a risk of an unsafe outcome, though it can create political pressures on the participants and raise the stakes, making it tempting to

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[81] Arthur Allen, *Op-Ed: While the U.S. Rushes to Develop a COVID-19 Vaccine, Here's What Science Tells Us*, LOS ANGELES TIMES (May 21, 2020), https://www.latimes.com/opinion/story/2020-05-21/coronavirus-vaccine-testing-approval.

[82] Luciano Borio, Scott Gottlieb, *A Fast Coronavirus Vaccine, Without Cutting Corners*, WALL STREET JOURNAL (May 31, 2020, 3:47 PM), https://www.wsj.com/articles/a-fast-coronavirus-vaccine-without-cutting-corners-11590954444?mod=opinion_lead_pos8.

[83] Ezekiel J. Emanuel and Paul A. Offit, *Could Trump Turn a Vaccine Into a Campaign Stunt?*, THE NEW YORK TIMES (June 8, 2020), https://www.nytimes.com/2020/06/08/opinion/trump-coronavirus-vaccine.html.

[84] Ian Sample, *UK plans £38m Centre to Start Production of Coronavirus Vaccine*, THE GUARDIAN (May 17, 2020), https://www.theguardian.com/society/2020/may/17/uk-plans-38m-centre-to-start-production-of-coronavirus-vaccine (in the UK); Christopher Rowland, et al., *Even Finding a Covid-19 Vaccine Won't Be Enough to End the Pandemic*, THE WASHINGTON POST (May 11, 2020), https://www.washingtonpost.com/business/2020/05/11/coronavirus-vaccine-global-supply/ (in the U.S.).

hide bad results. Such investments should be accompanied by careful oversight of the beneficiaries.

Another potential approach is to permit use through an Emergency Use Authorization (EUA) for vaccines that have successfully passed one or more stages of trial in some circumstances.[85] An Emergency Use Authorization requires a declaration by the Secretary of HHS that circumstances justify providing one, following a determination of a domestic, military, public health emergency or material threat. The Secretary should then consult "(to the extent feasible and appropriate given the applicable circumstances) with the Assistant Secretary for Preparedness and Response (ASPR), the Director of the National Institutes of Health (NIH), and the Director of CDC," and if the statutory criteria have been met, issue the authorization.
The criteria are:

> ...an EUA may be instituted for an unapproved medical product where there is a:
>
> 1. Serious or life-threatening illness or condition caused by CBRN agent as set forth in DHHS declaration;
>
> 2. Reasonable belief that the product may be effective in diagnosing, treating, or preventing the illness or condition caused by the agent (based on totality of scientific data);
>
> 3. The product's known and potential benefits outweigh known and potential risks when used for disease or condition; and
>
> 4. There is no adequate approved, available alternative.

This is an approach whose desirability really depends on the details. Vaccines have been approved for emergency use before, in analogous circumstances, though not through an EUA. For example, a meningococcal B vaccine licensed elsewhere but not in the United States was used during a meningococcal outbreak in several college campuses.[86] In 2014-2015, a vaccine not yet approved for Ebola was allowed use during an outbreak in Africa.[87] The vaccine was later approved.[88]

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[85] John D. Blum & Jordan Paradise, *Public Health Preparedness & Response: An Exercise in Administrative Law*, 20 DEPAUL J. HEALTH CARE L. 1, 1-3 (2019); Charles G. Kels, *Dispensing Medical Countermeasures: Emergency Use Authorities and Liability Protections*, 13 HEALTH SECURITY, 139 (2015).
[86] Blair Capitano, et al., *Experience Implementing a University-Based Mass Immunization Program in Response to a Meningococcal B Outbreak*, 15 HUMAN VACCINES & IMMUNOTHERAPIES, 717 (2019); JoNel Aleccia, *Emergency Meningitis Vaccine Will be Imported to Halt Ivy League Outbreak,* NBC NEWS (Nov. 15, 2013), https://www.nbcnews.com/healthmain/emergency-meningitis-vaccine-will-be-imported-halt-ivy-league-outbreak-2D11603651.
[87] Marissa Fritz, *Drug Approval During a Public Health Crisis*, THE REGULATORY REVIEW (Feb. 11, 2020), https://www.theregreview.org/2020/02/11/fritz-drug-approval-during-public-health-crisis/.
[88] *First FDA-Approved Vaccine for the Prevention of Ebola Virus Disease, Marking a Critical Milestone in Public Health Preparedness and Response*, U.S. FOOD & DRUG ADMINISTRATION (December 19, 2019), https://www.fda.gov/news-events/press-announcements/first-fda-approved-vaccine-prevention-ebola-virus-disease-marking-critical-milestone-public-health.

Both cases involved an outbreak of a potentially fatal disease, creating a vivid and visible life-threatening emergency. In the COVID-19 context, an example could be an outbreak overwhelming hospitals, as happened in, for example, Italy or New York City, or an outbreak in a high-risk environment like a nursing home.

The legitimacy of such an approach would also depend on the evidence on the potential benefits compared to the potential risks. The meningococcal B vaccine had undergone several clinical trials, and had been approved – and used – in Europe, after enough safety data was provided to European regulatory authorities to justify it, and during its use, no new safety concerns emerged.[89] The situation for Ebola vaccines was different. A candidate vaccine was given to "at-risk HCW/FLWs and at-risk adults and children during the 2014–2016 West African outbreak during clinical trials using investigational expanded access protocols," alongside a larger efficacy trial in Guinea that showed very high efficacy, justified by the severity of the disease.[90] During the 2018 and 2019 Ebola outbreaks in the Democratic Republic of Congo (DRC), the vaccine was not yet licensed, but there was the evidence of human trials supporting its use.[91] Even there, there was initial hesitancy to use the vaccine in lactating and pregnant women – in which the vaccine had not been tested – but the severity of the risks led to the vaccine being used in that population, after some debate.[92] Similar questions about use of COVId-19 vaccines in pregnancy can come up in the U.S. - the FDA is reluctant to allow trials in pregnant women, and for COVID-19 there is no special reason to deviate from that rule, but there could be a question about making these vaccines available to that population without such trials.[93]

In other words, emergency use decisions depend not only on the existence of an emergency, but also on other factors such as the danger from the disease and the already existing data on the vaccine. Both Ebola and meningococcal disease have higher rates of mortality than COVID-19, and meningococcal has a substantial risk of long-lasting disability even in survivors. Allowing emergency use of a vaccine with very little safety data may be less likely for COVID-19 – but that balance may shift as more data accumulates. An obvious concern there is that political pressures will lead to approval of emergency use of COVID-19 where there is no objective justification. Arguably, that has already happened with HCQ.[94]

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[89] JoNel Aleccia, *Emergency Meningitis Vaccine Will be Imported to Halt Ivy League Outbreak,* NBC NEWS (Nov. 15, 2013), https://www.nbcnews.com/healthmain/emergency-meningitis-vaccine-will-be-imported-halt-ivy-league-outbreak-2D11603651.

[90] Jenny A. Waldorf, et al., *Considerations for Use of an Ebola Vaccine During an Emergency Response*, 37 VACCINE 7190, 7195 (2019).

[91] *Second Ebola Vaccine to Completement "Ring Vaccination" Given Green Light in DRC*, WORLD HEALTH ORGANIZATION (Sept. 23, 2019), https://www.who.int/news-room/detail/23-09-2019-second-ebola-vaccine-to-complement-ring-vaccination-given-green-light-in-drc.

[92] Archana Asundi, Nahid Bhadelia, *Making Emergency Use of Experimental Vaccines Safer*, 22 AMA J. OF ETHICS 43, 44 (2020).

[93] Sam F. Halabi, *Zika and the Regulatory Regime for Licensing Vaccines for use During Pregnancy*, 26 ANN. HEALTH L. 20 (2017).

[94] John Timmer, *FDA Approves the Emergency Use of Chloronique for COVID-19*, ARSTECHNICA (Mar. 31, 2020), https://arstechnica.com/science/2020/03/fda-approves-the-emergency-use-of-chloroquine-for-covid-19/; Nicholos Florko, *Why Was an Obscure Federal Bureaucrat Involved in Trump's Emergency Hydroxychloroquine Authorization*, STAT NEWS (April 4, 2020), https://www.statnews.com/2020/04/24/why-rick-bright-involved-hydroxychloroquine/ (supporting the view that this was unjustified comes from the FDA's warning against use of the drug outside hospital settings, issued less than a month after the emergency use authorization); *FDA Cautions Against Use of Hydroxychloroquine or Chloroquine for COVID-19 Outside of the Hospital Setting or a Clinical Trial Due to Rusk of Heart Rhythm Problems*, U.S. FOOD & DRUG ADMINISTRATION (last visited June 19, 2020),

Other steps that can and should happen early are setting up workgroups by the different oversight committees once vaccine candidates advance in the trials. The NIH has already set up multiple expert committees working on the different steps.[95] ACIP, as mentioned, has set up a workgroup to monitor COVID-19 Vaccines in April 2020.

More controversial is the question of whether to allow challenge/rechallenge trials.[96] Challenge/rechallenge trials involve intentionally exposing consenting volunteers who received the vaccine to the virus: injecting them with live COVID-19 virus, under medical supervision. This has the advantage of not depending on the trial participants being exposed to Covid-19 naturally – something that could take time, especially in areas where the pandemic is under control, and especially if the virus is less prevalent during the summer. Several experts strongly recommend it.[97] They point out that by limiting the tests to young volunteers, the risk can be kept very low, and the benefits of having a vaccine sooner are meaningful, including in terms of lives saved.[98] The problem, as set out by some of these authors, is that these trials are asking people to "take on risk of severe illness or death."[99] This is especially true since there is much we do not yet know about COVID-19, and there is no good treatment for it.[100] Nonetheless, supporters argue these trials will save lives.[101] Volunteers are lining up for it: a grassroots hotline has signed up thousands of people saying they are willing to take the risk (though such signing up is no substitute for a full informed consent process).[102]

Another challenge is that to be ethical, challenge/rechallenge studies should consist of healthy, young volunteers - people for whom the risks of Covid-19 are low. But results in such volunteers would not necessarily teach us about the effect of tested vaccines in high-risk populations, such as the elderly. For example, influenza vaccines are much less effective in older people than in

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https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or.

[95] *Leadership*, NATIONAL INSTITUTES OF HEALTH (June 9, 2020), https://www.nih.gov/research-training/medical-research-initiatives/activ/leadership.

[96] *Vaccine Challenge Studies – Can it Speed up Coronavirus Vaccine Licensing*, SKEPTICAL RAPTOR (April 20, 2020), https://www.skepticalraptor.com/skepticalraptorblog.php/vaccine-challenge-studies-can-it-speed-up-coronavirus-vaccine-licensing/.

[97] Stanley A. Plotkin & Arthur Caplan, *Extraordinary Diseases Require Extraordinary Solutions*, 38 VACCINE 3987 (2020), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7167540/; Nir Eyal, et al., *Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure*, 221 J. OF INFECTIOUS DISEASES 1752 (2020).

[98] Stanley A. Plotkin & Arthur Caplan, *Extraordinary Diseases Require Extraordinary Solutions*, 38 VACCINE 3987 (2020), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7167540/

[99] Nir Eyal, et al., *Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure*, 221 J. OF INFECTIOUS DISEASES 1752 (2020).

[100] Shayla Love, *People Are Willing to Risk Their Lives for a COVID Vaccine. Should We Let Them?*, VICE (April 28, 2020, 4:00 AM), https://www.vice.com/en_us/article/5dm7na/why-intentionally-infecting-people-with-coronavirus-could-be-worth-it; Carolyn Y. Johnson, *Inside the Extraordinary Race to Invent a Coronavirus Vaccine*, THE WASHINGTON POST (May 3, 2020, 12:56 PM), https://www.washingtonpost.com/science/2020/05/02/coronavirus-vaccine/.

[101] Stanley A. Plotkin & Arthur Caplan, *Extraordinary Diseases Require Extraordinary Solutions*, 38 VACCINE 3987 (2020); Nir Eyal, et al., *Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure*, 221 J. OF INFECTIOUS DISEASES 1752 (2020).

[102] Josh Morrison, *Challenge Trials can Speed Development of a Covid-19 Vaccine. Planning for them Needs to Start Now*, STAT NEWS (May 28, 2020), https://www.statnews.com/2020/05/28/challenge-trials-speed-development-covid-19-vaccine-start-planning-now/.

younger ones, and special variations of them have been developed for that population.[103] Similarly, the fact that Covid-19 vaccines are shown to be effective in young volunteers in challenge/rechallenge studies would not automatically mean they can protect the older population, those that are most at risk of harm from the disease. Another potential risk raised is that a setback during the challenge/rechallenge trials such as the death of a participant from COVID-19 could undermine vaccine development – even if it's not directly because of the vaccine.[104]

Highly problematic would be allowing emergency use authorization based on antibodies data alone. At this point, it is not clear what level of antibodies protects against severe COVID-19 disease, what level protects against infecting others – the link between antibody levels and protection can be complex, and we do not yet have that data for COVID-19 vaccines, so acting on that alone can lead to unsupported decisions.

Additionally uncertain is the mutation rate and effect on the virus, both of which can contribute to a less viable new vaccine. If a mutation is more infectious than another, the vaccine may not be targeting the more virulent form of the virus. If the mutation rate is much higher than predicted, then a vaccine could be ineffective within a year or even just a few months.

Just as problematic would be committing too soon to one company: we do not yet know which vaccine candidate will succeed in the trials. The UK may have done that: the government committed large sums of money to production of one candidate vaccine that is still in early stages of testing.[105]

Similarly, skipping steps in testing would increase the risks of bad safety outcomes and may undermine the use of even a plausibly safe vaccine by decreasing trust. Going to human studies without animal studies would not necessarily mean that the final vaccine is unsafe.[106] If enough testing in humans is done, we can still end up with good data on safety and effectiveness. But it could mean that risks that could be discovered before humans were given the vaccine were not discovered - creating additional risks for trial volunteers, and vulnerability to misuse of that fact by vaccine opponents seeking to present all vaccines as unsafe.

Another potential problem that needs to be avoided is lack of transparency. Oversight and advisory committees involved in the vaccine process – the regular committee, and those created

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[103] M. Alexander Otto, *MMWR: Current Fly Vaccine Does Not Protect Elderly*, MD EDGE (Feb. 15, 2018), https://www.mdedge.com/jcomjournal/article/158749/influenza/mmwr-current-flu-vaccine-does-not-protect-elderly; *see generally Vaccine Effectiveness: How Well do the Flu Vaccines Work*, CENTERS FOR DISEASE CONTROL AND PREVENTION, https://www.cdc.gov/flu/vaccines-work/vaccineeffect.htm#older-vaccinated.

[104] This, and other points, were raised by Dr. Michael Rosenblatt: Michael Rosenblatt, *Human Challenge Trials with Live Coronavirus Aren't the Answer to a Covid-19 Vaccine,* STATNEWS (June 23, 2020) available at: https://www.statnews.com/2020/06/23/challenge-trials-live-coronavirus-speedy-covid-19-vaccine/?fbclid=IwAR069niKXXJI8BkCSnspz78DhyHPcoi8HJyfhJRKW7j1WacM2PTL3YDkq60

[105] Ian Sample, *UK plans £38m Centre to Start Production of Coronavirus Vaccine*, THE GUARDIAN (May 17, 2020), https://www.theguardian.com/society/2020/may/17/uk-plans-38m-centre-to-start-production-of-coronavirus-vaccine.

[106] Nicoletta Lanese, *Researches Fast-Track Coronavirus Vaccine by Skipping Key Animal Testing First*, LIVE SCIENCE (March 13, 2020), https://www.livescience.com/coronavirus-vaccine-trial-no-animal-testing.html (one of the vaccine candidates skipped animal trials).

to focus on a COVID-19 vaccine – need full, transparent information, to do their job of meaningful oversight and help lead us to a vaccine that is, in fact, safe and effective.

PART IV: MESSAGING CHALLENGES

Public trust is crucial in a pandemic; if the state wants to impose broad-reaching measures, it has to rely either on broad voluntary compliance or on very aggressive measures, which are costly and not always available or effective.[107] When it comes to a vaccination program, messaging matters. In relation to the COVID-19 vaccine, we face at least three potential messaging problems:

(1) Overselling: hyping the data, creating excessive expectations that will then have to be corrected, undermining trust;
(2) Undershowing: not being transparent enough about what is being done to ensure safety; not providing people enough information about the process and results, so that people may mistrust even a vaccine that actual data shows is safe and effective;
(3) Enabling misinformation, including by leaving false messages without a counter.

As of June 2020, we have already seen several examples of overselling vaccines results, with potentially bad consequences. Early results published by Moderna, a company producing one of the vaccine candidates, led to headlines strongly suggesting that the vaccine was effective.[108] Very quickly, scientists spoke up to caution against over extrapolating from these press releases.[109] Among the problems is the fact that out of 45 participants in the trial, Moderna provided data only on eight who developed an antibody response, raising the question of what did the data from the other participants showed.[110] Some of the data was provided later, but there were still questions on whether the results were overhyped, and much is still unknown.[111] The

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[107] Jay J. Van Bavel, et al., *Using Social and Behavioural Science to Support COVID-19 Pandemic Response*, 4 NATURE HUMAN BEHAVIOUR (2020), 460, https://www.nature.com/articles/s41562-020-0884-z.
[108] Elizabeth Cohen, *Early Results From Moderna Corovavirus Vaccine Trial Show Participants Developed Antibodies Against the Virus*, HENRY HERALD (May 18, 2020), https://www.henryherald.com/features/health/early-results-from-moderna-coronavirus-vaccine-trial-show-participants-developed-antibodies-against-the-virus/article_d2ed3d50-c253-5650-a259-56836ab254ce.html https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-positive-interim-phase-1-data-its-mrna-vaccine; Helen Branswell, *Vaccine Experts Say Moderna Didn't Produce Data Critical to Assessing Covid-19 Vaccine*, STATNEWS (May 19, 2020), https://www.statnews.com/2020/05/19/vaccine-experts-say-moderna-didnt-produce-data-critical-to-assessing-covid-19-vaccine/.
[109] Helen Branswell, *Vaccine Experts Say Moderna Didn't Produce Data Critical to Assessing Covid-19 Vaccine*, STAT NEWS (May 19, 2020), https://www.statnews.com/2020/05/19/vaccine-experts-say-moderna-didnt-produce-data-critical-to-assessing-covid-19-vaccine/; *Moderna Coronavirus Vaccine – Tempering the Breathless Pharma Hype*, SKEPTICAL RAPTOR (May 19, 2020), https://www.skepticalraptor.com/skepticalraptorblog.php/moderna-coronavirus-vaccine-tempering-breathless-pharma-hype/.
[110] Helen Branswell, *Vaccine Experts Say Moderna Didn't Produce Data Critical to Assessing Covid-19 Vaccine*, STAT NEWS (May 19, 2020), https://www.statnews.com/2020/05/19/vaccine-experts-say-moderna-didnt-produce-data-critical-to-assessing-covid-19-vaccine/; Jonathan Gardner, *More Questions Than Answers as Moderna's Coronavirus Vaccine Speeds Ahead*, BIOPHARMA DIVE (May 19, 2020), https://www.biopharmadive.com/news/moderna-coronavirus-vaccine-data-more-questions/578229/.
[111] Carolyn Y. Johnson, *Moderna's Coronavirus Vaccine Shows Encouraging Early Results*, THE WASHINGTON POST (May 19, 2020), https://www.washingtonpost.com/health/2020/05/18/coronavirus-vaccine-first-results/; Matt Egan & Robert Kuznia, *Moderna's Coronavirus Vaccine Announcement Set Off a Frenzy on Wall Street. Now Some*

fact that Moderna's executives sold large amounts of their stock in the company for large profits did not increase confidence, either.[112] Similarly, results from the UK vaccine trials appear to have, initially, been overstated. What was first touted as success in making monkeys immune was later questioned, as the vaccine appeared to prevent pneumonia in the monkeys but not infection, thus – suggesting the vaccine would not prevent spread of disease.[113] These situations – of initial promising press releases following by dampening down – could lead to loss of trust. Dr. Paul Offit, a vaccine expert, described it as "science by press release", and pointed out the risk of speaking up before there is sufficient data.[114]

Another potential problem is when the public is not informed on how safety is monitored and overseen. For example, while vaccine experts know that there are multiple oversight committees and multiple monitoring systems to evaluate vaccine safety, the public does not – and should. Even in regular times, not enough is made public about the extensive institutional arrangements surrounding vaccines. That is not because the information is not out there; it's likely simply that technical bureaucratic details do not make for a good story, even if they are very, very important. In relation to COVID-19 vaccines, too, more information about the process would be useful. For example, Dr. Paul Offit has mentioned publicly the existence of an NIH committee and the mobilization to prepare for large trials. But the administration has not publicized it, and it should. Being front and center about the steps taken to assure the safety of a new vaccine would help build public confidence.

Problems need to be stated openly, and the steps taken to address them need to be openly said, too. For example, in the high-dose group of Moderna's trial about 25% of recipients had a fever and flu-like symptoms.[115] Moderna has decided not to use that high dose. But that information was not included in the press release, and was later published by journalists.[116] This can make it appear like problems were swept under the carpet – and create unnecessary mistrust. Much better to openly describe any issues. The company – or government oversight officials - can explain why this would not, necessarily, be a deal breaker: a few days of flu-like symptoms might still leave a vaccine with a favorable risk/benefit balance. In this case, the company has also already decided not to use the dose that created this risk, anyway, out of an abundance of caution. Open,

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are Calling for an Investigation, CNN BUSINESS (June 1, 2020), https://www.cnn.com/2020/06/01/business/moderna-vaccine-stock-sales-invs/index.html.

[112] Damian Garde, *Moderna Executives Have Cashed Out $89M in Shares This Year, as Stock Price has Soared on Vaccine Hopes*, STAT NEWS (May 27, 2020), https://www.statnews.com/2020/05/27/moderna-executives-cashed-out-shares-stock-price-soared/.

[113] Rachel Schraer, *Coronavirus Vaccine: Macaque Monkey Trial Offers Hope*, BBC NEWS (May 15, 2020), https://www.bbc.com/news/health-52674739 (first); Andy Gregory, *Coronavirus: Scientists Warn Oxford Vaccine May Only Offer 'Partial Protection' After Results of Monkey Trial*, INDEPENDENT (May 19, 2020), https://www.independent.co.uk/news/health/coronavirus-vaccine-oxford-trials-concerns-transmission-astrazeneca-latest-a9521241.html (later); *see generally* Ewen Callaway, *Coronavirus Vaccine Trials Have Delivered Their First Results – But Their Promise is Still Unclear*, NATURE (May 19, 2020), https://www.nature.com/articles/d41586-020-01092-3.

[114] Jonathan Gardner, *More Questions Than Answers as Moderna's Coronavirus Vaccine Speeds Ahead*, BIOPHARMA DIVE (May 19, 2020), https://www.biopharmadive.com/news/moderna-coronavirus-vaccine-data-more-questions/578229/.

[115] Matthew Herper, *He Experienced a Severe Reaction to Moderna's Covid-19 Vaccine Candidate. He's Still a Believer*, STAT NEWS (May 26, 2020), https://www.statnews.com/2020/05/26/moderna-vaccine-candidate-trial-participant-severe-reaction/

[116] *Id*.

transparent communication could help build trust – and avoid making a non-issue something those seeking to create mistrust can build on.

Finally, steps need to be taken to prepare to respond to anti-vaccine misinformation about a new vaccine. Anti-vaccine groups have already started preparing the ground to create mistrust, or build on natural mistrust for a new vaccine or as a result of the previously mentioned issues.[117] This is not the only type of Coronavirus misinformation being spread, but it's part of it, and needs to be countered. In part, addressing the issues above can reduce the fertile ground available for those seeking to create mistrust. But it's not enough. Responses must be prepared to points of misinformation, and shared fast. For example, the movie Plandemic was aggressively and cleverly spread by anti-science groups on social media.[118] But responses were quickly created and shared in social media.[119] It would have been better to preempt and respond to the misinformation before it spread. But at the very least, misinformation about COVID-19 vaccines should not be left unanswered.

CONCLUSION:

COVID-19 turned our world upside down. Many are desperately awaiting a vaccine. But we should be cautious not to take steps on the way to the vaccine that will make the situation worse, or not improve it.

Nor are the substantive pressures to prevent harms the only risk. In a recent editorial, scientist Paul Offit and oncologist Zeke Emanuel sounded a caution against potential political intervention in COVID-19 vaccine development:

> … the F.D.A. could issue an Emergency Use Authorization for one or more vaccines. These authorizations only require that the F.D.A. finds it "reasonable

[117] Bennie Badger, FACEBOOK (May 26, 2020, 10:29 PM), https://www.facebook.com/hu.suc/posts/10157154200392551; Hear This Well, FACEBOOK (May 23, 2020 at 10:26 AM), https://www.facebook.com/HearThisWell/posts/3213865541990895; Joshua Coleman, *Coronavirus and What We Do Next*, FACEBOOK (March 18, 2020), https://www.facebook.com/JoshBucky/videos/10221388003307534/?eid=ARArxf7c-c4y1bFkD7p3lpVY3BAPnDBgwxOrhrb4xaGugzOjF6d1x1kF-3bErhs1qq0ljDE-vlK349tg&hc_ref=ARSArxkkspq98JKQfzlb-T-eKQLvJdQhkuwJ24Dv7Q9OE6Ipq3HyOQDdYYjo2F-ipZI&__xts__[0]=68.ARACpyVexqNdIXQj-ZbYGJ0ZiERk3p5mFsslwQzxPmj5ZnWHCGRcAN2us2ok5QC6ffJmtRiM6eVNjLq4AuKfOQutOUy6zZCS7RxEqpgSP9563vHsT4l3Nitn3sm5dz2vFOO-UgX2EGp2xyYltKAT60WNMf5ltsHVQktrhZtW_2N-bsSDXEDR8iQSRvgAGpbqJg_csNAm1t4nwPw-KYM05ShrlBGRSoag2o4BlqB_MycuiYyGlX4ElDtR-R8T_BInGtcEsbDfFGtln4kms2kTZAhn3Y_uYFj68k-CPRQndgwNVOwQN9QD6680kWOKKtcHaykcwb4Fb8SavyL2qTSqTBqZ_65YLwNKAUoITg.

[118] Renee DiResta & Isabella García-Camargo, *Virality Project (US): Marketing Meets Misinformation*, STANFORD INTERNET OBSERVATORY (May 26, 2020), https://cyber.fsi.stanford.edu/io/news/manufacturing-influence-0?fbclid=IwAR39LlFmXSHY6rQ36c804KOBkpIFgSKAv_eKJojooAI81KvJ3GMsbQ91ExY.

[119] Liz Ditz, *Judy Mikovits: Not a Reliable Source of Information on COVID19, Vaccines, or Anything in Science*, I SPEAK OF DREAMS (May 8, 2020), https://lizditz.typepad.com/i_speak_of_dreams/2020/05/judy-mikovits-not-a-reliable-source-of-information-on-covid19-vaccines-or-anything-in-science.html (containing a list of responses).

> to believe" that a vaccine "may be effective" in preventing a life-threatening disease for it to be put on the market, without being formally licensed.
>
> An emergency authorization would allow Mr. Trump to hold his news conference and declare victory. But like President George W. Bush's "Mission Accomplished" proclamation, it has the potential to be a travesty. Millions of vaccines could be distributed without proof that the vaccine can prevent disease or transmission.
>
> . . .
>
> Thousands of Americans have already died as Donald Trump has perpetually postponed effective public health interventions and made poor therapeutic recommendations. We must be on alert to prevent him from corrupting the rigorous assessment of safety and effectiveness of Covid-19 vaccines in order to pull an October vaccine surprise to try to win re-election.[120]

Practical and political pressures can combine to push to inappropriately rushed vaccine development – and can backfire.

We have a remarkable system for testing vaccines and monitoring their safety, and we should let it work in this case, too. While we should make adjustments where we can do so without sacrificing safety, we should make sure we are, indeed, not sacrificing safety or effectiveness.

[120] Ezekiel J. Emanuel & Paul A. Offit, *Could Trump Turn a Vaccine Into a Campaign Stunt?*, THE NEW YORK TIMES (June 8, 2020), https://www.nytimes.com/2020/06/08/opinion/trump-coronavirus-vaccine.html (concerning politicizing the process).

Appendix A: COVID-19 Vaccine Candidates in Trials[121]

Company	Vaccine Candidate	Type of Vaccine	Stage in Trials
1. AIVITA Biomedical, Inc.	AV-COVID-19	A dendritic cell vaccine: using a type of immune cell whose function is to present the antigens we want the body to learn to protect against to other immune cells that can then create antibodies to them. This technology is not currently in use for preventing vaccines.	Phase I/II clinical trial
2. Biontech RNA Pharmaceuticals GmbH	BNT162a1, BNT162b1, BNT162b2, BNT162c2	mRNA vaccine: messenger RNA is a technology involving inserting messenger RNA into the body to "kickstart the endogenous production of proteins similar enough to the virus on RNA to that they trigger the body's adaptive immune system to produce antibodies effective against the actual target".[122] The technology has been in existence for years, but no licensed vaccines currently use it.	Phase I/II clinical trial
3. CanSinoBiologics	Ad5-nCoV	This is a recombinant novel coronavirus vaccine that incorporates the adenovirus type 5 vector (Ad5). That means the relevant part of the virus was genetically engineered onto a different virus that infects the body, an adenovirus that was itself modified so it cannot replicate in humans, in the hope that the immune response to it would	Phase I clinical trial

[121] *Coronavirus Vaccine Trials – Updating Current Studies Across the World*, Skeptical Raptor (June 9, 2020), https://www.skepticalraptor.com/skepticalraptorblog.php/coronavirus-vaccine-trials-updating-current-studies-across-world/ (This table has been updated up to the stage this article has been submitted. Obviously, this is a fast-moving area and the article will, at some point, be published. Sections of the table were directly copied from the post. Note: the post includes a discussion of several trials of BCG vaccines that are being studied as a potential treatment for COVID-19. Because these are not vaccines examined to prevent the disease, they are not included in this table, but they are described in the post.)

[122] *Id*.

		include the relevant parts of the virus.	
4. Clover Biopharmaceuticals AUS Pty Ltd	SCB-2019 trimeric S-subunit protein	This is a recombinant subunit vaccine for COVID-19. Clover's vaccine utilizes an S-Trimer subunit that resembles the native trimeric viral spike protein via a mammalian cell-culture production system.	Phase I/II clinical trial
5. Immunitor LLC	V-SARS	A "pill of therapeutic vaccine made from heat-inactivated plasma from donors with COVID-19."[123]	Phase I clinical trial
6. Inovio Pharmaceuticals	INO-4800	This is a DNA vaccine, which is a new approach and not currently in use in routine vaccines. (Note: all this means is that this is new. It is not a comment about the value of the technology).[124]	Phase I clinical trial
7. Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China	CTII-nCoV	This is another recombinant vaccine using adenovirus 5 to deliver a spike protein of the virus, which the immune system will then create a response to. [125]	Phase I/II clinical trial
8. Jenner Institute – the University of Oxford	ChAdOx1	The vaccine "uses a replication-deficient chimpanzee adenovirus to deliver a SARS-CoV-2 protein to induce a protective immune response."[126]	Phase I/II clinical trial

[123] *Tableted COVID-19 Therapeutic Vaccine (COVID-19)*, CLINICALTRIALS.GOV (May 8, 2020), https://clinicaltrials.gov/ct2/show/NCT04380532.
[124] *INO-4800 DNA Coronavirus Vaccine*, PRECISION VACCINATIONS (June 8, 2020), https://www.precisionvaccinations.com/vaccines/ino-4800-dna-coronavirus-vaccine (this is information provided by the company).
[125] *A Phase II Clinical Trial to Evaluate the Recombinant Vaccine for COVID-19 (Adenovirus Vector) (CTII-nCoV)*, CLINICALTRIALS.GOV (April 10, 2020), https://clinicaltrials.gov/ct2/show/NCT04341389.
[126] *Investigational ChAdOx1nCoV-19 Vaccine Protects Monkeys Against COVID-19 Pneumonia*, NATIONAL INSTITUTES OF HEALTH (May 15, 2020), https://www.nih.gov/news-events/news-releases/investigational-chadox1-ncov-19-vaccine-protects-monkeys-against-covid-19-pneumonia.

9. Moderna Therapeutics	mRNA-1273	mRNA vaccine: messenger RNA is a technology involving inserting messenger RNA into the body to "kickstart the endogenous production of proteins similar enough to the virus on RNA to that they trigger the body's adaptive immune system to produce antibodies effective against the actual target".[127] The technology has been in existence for years, but no licensed vaccines currently use it.	Phase I clinical trial
10. Novavax	NVX-CoV2373	This is a genetically-engineered nanoparticle vaccine using a Matrix-M adjuvant, a new adjuvant.[128]	Phase I/II clinical trial
11. Shenzhen Geno-Immune Medical Institute	LV-SMENP-DC	This is a synthetic minigene[129] that has been engineered based on conserved domains of the viral structural proteins and a polyprotein protease.	Phase I/II clinical trial
12. Sinovac Biotech Co., Ltd	inactivated SARS-CoV-2 vaccine	Inactivated vaccine – a more traditional technology, which takes the SARS-CoV-2 virus and inactivates it – "kills" it, stops it from replicating – using chemical agents, like the injected influenza vaccine or polio vaccine.	Phase I/II clinical trial
13. Symvivo Corporation	oral bacTRL-Spike	This vaccine uses oral probiotics – harmless or benign bacterial – to deliver the spike protein to the	Phase I clinical trial recruiting

[127] *Coronavirus Vaccine Trials – Updating Current Studies Across the World*, SKEPTICAL RAPTOR (June 9, 2020), https://www.skepticalraptor.com/skepticalraptorblog.php/coronavirus-vaccine-trials-updating-current-studies-across-world/.
[128] *Matrix-M Adjuvant Technology*, NOVAVAX, (last visited June 22, 2020), https://novavax.com/page/10/matrix-m-adjuvant-technology.
[129] *Minigene*, WIKIPEDIA (last visited June 22, 2020), https://en.wikipedia.org/wiki/Minigene.

		immune system, to trigger an immune response.	