2

Global Medical War Chest

Lawrence O. Gostin

China's release of genomic sequencing data for SARS-CoV-2 on January 11, 2020 was the start of a race to develop vaccines and other medical countermeasures for COVID-19. The Coalition for Epidemic Preparedness Innovations (CEPI) quickly contacted its partners that were developing novel platforms that could be adapted to new pathogens and offered financial support to direct their efforts to SARS-CoV-2.[1] Less than ten weeks later, on March 16, Moderna's vaccine candidate entered a phase 1 clinical trial, and on July 27 it entered phase 3.[2] The vaccine candidate – a novel messenger RNA (mRNA) vaccine – was based on a similar vaccine Moderna had been developing for MERS. Biotech companies from around the globe also launched clinical trials of SARS-CoV-2 vaccine candidates. China and Russia began deploying their vaccines for selected populations even before Phase 3 trials were completed. By December 2, the United Kingdom granted approval for another mRNA vaccine manufactured by Pfizer/BioNTech, with US approval for both mRNA vaccines following closely behind.[3] By December 29, the UK approved yet another vaccine developed by AstraZeneca/Oxford. In just one year, scientists from around the world developed safe and effective vaccines against COVID-19, a triumph that is unprecedented in human history.

How was it possible to develop COVID-19 vaccines at "pandemic" speed? Scientific understanding and technologies for genomics and structural biology have exploded. High-income countries and biotech companies also had clear incentives

[1] Nicole Lurie, Melanie Saville, Richard Hatchett & Jane Halton, *Developing Covid-19 Vaccines at Pandemic Speed*, NEJM (Mar. 30, 2020).

[2] Moderna, Moderna's Work on a Potential Vaccine against COVID-19, www.modernatx.com/modernas-work-potential-vaccine-against-covid-19 (last visited Feb. 5, 2023).

[3] Jonathan Corum, Denise Grady, Sui-Lee Wee & Carl Zimmer, *Coronavirus Vaccine Tracker*, N.Y. Times (Aug. 31, 2022), www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html (last visited Feb. 5, 2023).

to invest substantially in COVID-19 vaccine development, given the global spread of the virus and its massive health, economic, and social impacts.

The COVID-19 pandemic overwhelmed the world's capacity to respond effectively. Non-therapeutic interventions (such as masks, distancing, and stay-at-home orders) failed to keep the virus under control in most countries. Vaccines became the only way to return to a semblance of normalcy, with schools and businesses fully open, people socializing, and travel resuming.

Previous Ebola outbreaks demonstrated the difference that a timely vaccine can make in confronting a deadly threat – and the factors that contribute to costly vaccine development delays.

The Ebola epidemic in the Democratic Republic of the Congo (DRC) began on August 1, 2018, ending two years later on June 25, 2020. The epidemic was particularly challenging because it took place in an active conflict zone.[4] Were it not for the deployment of a promising vaccine, rVSV-ZEBOV, the death toll would have been far greater.[5] The vaccine was administered in rings to high-risk individuals who were geographically or socially connected to patients: contacts, contacts of contacts, and frontline responders. The vaccine proved effective, building on evidence gathered from Guinea in 2015. In both outbreaks, researchers found that vaccinated individuals did not contract the Ebola virus.[6]

The rVSV-ZEBOV vaccine was not new. The Public Health Agency of Canada applied for a patent on the vaccine in 2003.[7] But the first human clinical trial didn't begin until over a decade later when the West African Ebola crisis finally spurred action. NewLink Genetics commenced a phase 1 clinical trial in 2014, supported by the National Institutes of Health (NIH) and US Department of Defense.[8] NewLink then licensed vaccine rights to Merck Pharmaceuticals, which pushed the vaccine into additional clinical trials. In late 2019, the vaccine would ultimately become the

[4] WHO, Timeline of the Ebola Outbreak Response in Democratic Republic of the Congo 2018, www.who.int/ebola/drc-2018/timeline/en/ (last visited Feb. 5, 2023).

[5] Jon Cohen, *Congo's Ebola Outbreak Is All but Over. Did an Experimental Vaccine Help?*, Science (Jul. 18, 2018), www.science.org/content/article/congo-s-ebola-outbreak-all-over-did-experimental-vaccine-help (last visited Feb. 5, 2023).

[6] Ana Maria Henao-Restrepo et al., *Efficacy and Effectiveness of an rVSV-Vectored Vaccine Expressing Ebola Surface Glycoprotein: Interim Results from the Guinea Ring Vaccination Cluster Randomized Trial*, The Lancet (Aug. 29, 2015), www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)61117-5/fulltext (last visited Feb. 5, 2023).

[7] Steven M. Jones et al., *Live Attenuated Recombinant Vaccine Protects Nonhuman Primates against Ebola and Marburg Viruses*, Nat. Med. (Jul. 2005), at 786–790; PCT/CA2003/001125 (published Feb. 5, 2004); Denise Grady, *Ebola Vaccine, Ready for Test, Sat on the Shelf*, N.Y. Times (Oct. 23, 2014), www.nytimes.com/2014/10/24/health/without-lucrative-market-potential-ebola-vaccine-was-shelved-for-years.html (last visited Feb. 6, 2023).

[8] Jason A. Regules et al., *A Recombinant Vesicular Stomatitis Virus Ebola Vaccine*, NEJM (2017), at 330–341.

first Ebola vaccine to be approved by regulators in Europe and by the US Food and Drug Administration (FDA).[9]

Why did such a promising vaccine with the potential to save thousands of lives languish for years? The intellectual property (IP) system does not generally incentivize companies to produce vaccines or medicines intended for small or uncertain markets. With vaccines costing millions of dollars to bring to the market, pharmaceutical companies, largely located in high-income countries, hesitated to invest in vaccine candidates intended primarily for low-income countries or sporadic outbreaks of diseases.[10]

The devastating West African Ebola epidemic galvanized political will and funding for Ebola research and development (R&D), which more than tripled from 2014 to 2015.[11] While the US government provided the majority of resources for Ebola and other viral hemorrhagic fevers, funding from private industry increased seven-fold.[12] Merck donated vaccine doses, while the Vaccine Alliance (Gavi) provided $1 million for operational costs.[13] The DRC, supported by the World Health Organization (WHO), Médecins Sans Frontières (MSF), and the United Nations Children's Fund (UNICEF), implemented ring vaccinations.[14] Governments, international organizations, public–private partnerships, and nongovernmental organizations (NGOs) offered additional support.[15]

Vaccines and medicines are essential components of our medical war chest. The Ebola vaccine development highlights how promising technologies can languish due to lack of funding and political attention. But it also demonstrates how we can

[9] Elizabeth Payne, *The Story of "the Canadian Vaccine" that Beat Back Ebola*, Nat'l Post (Sep. 4, 2016), https://nationalpost.com/news/canada/the-story-of-the-canadian-vaccine-that-beat-back-ebola (last visited Feb. 5, 2023).

[10] F. E. André, *How the Research-Based Industry Approaches Vaccine Development and Establishes Priorities*, 10 Dev. in Biologicals (2002), at 25–29.

[11] Nick Chapman et al., *Neglected Disease Research and Development: A Pivotal Moment for Global Health*, Policy Cure Research (Jan. 2019), at 6, www.policycuresresearch.org/wp-content/uploads/2019/01/Y9-GFINDER-full-report-web.pdf (last visited Feb. 5, 2023).

[12] Nick Chapman et al., *Neglected Disease Research and Development*, G-Finder (2015), at 4, 6.

[13] Jon Cohen, *Research during Ebola Vaccine Trial: It's Complicated*, Science (May 25, 2018), www.science.org/content/article/research-during-ebola-vaccine-trial-it-s-complicated (last visited Feb. 5, 2023).

[14] Ring vaccination is a disease control or vaccination strategy that health authorities implement during outbreaks. The purpose is to limit the spread of disease by vaccinating confirmed patients and those most likely to be infected by the patient. These persons comprise (i) those in close contact with the patient (primary contacts, such as family members, close friends, associates, health workers), (ii) those in close contact with the primary contacts (secondary contacts), and so on. By this strategy, all persons exposed to or who could have been exposed to the case are vaccinated, creating a "ring" or buffer of protection around the case, thereby limiting transmission. See www.ncbi.nlm.nih.gov/pmc/articles/PMC6149944/ (last visited Jan. 15, 2024).

[15] WHO, *WHO Supports Ebola Vaccination of High Populations in the Democratic Republic of the Congo* (May 21, 2018), www.who.int/news-room/detail/21-05-2018-who-supports-ebola-vaccination-of-high-risk-populations-in-the-democratic-republic-of-the-congo (last visited Feb. 5, 2023).

overcome market disincentives through targeted financing and partnerships to harness varied expertise. The COVID-19 pandemic was a game changer, demonstrating scientific prowess beyond what would have seemed possible.

This chapter explores the gap between technology's promise and our ability to realize the global public goods of vaccines and medicines. This gap stems from significant market disincentives in the R&D process, along with clinical trial challenges and regulatory hurdles. Yet a range of innovative financing strategies to delink R&D costs from vaccine and drug prices, along with well-designed and ethically run clinical trials, can fill this gap, facilitating development of urgently needed medical countermeasures.

1 WHY OUTBREAK DISEASE RESEARCH CAN FALTER AND FAIL

In 2018, the WHO identified eight priority diseases (including Ebola virus disease, SARS, and Zika) that warranted accelerated R&D given their epidemic potential, and the absence of efficacious medical countermeasures.[16] In many cases, development of countermeasures for these diseases has stalled at the clinical testing phase.[17]

Given that billions of dollars are spent on pharmaceutical research each year, what explains the lack of medical countermeasures for outbreak diseases? At its core, it's a question of market incentives: R&D is expensive and the market for technologies to fight infectious diseases with epidemic potential is often small and uncertain. Even with a predictable market of consumers in high-income countries, the process of bringing a new health product to market is expensive and time-consuming. Including out-of-pocket expenses and opportunity costs, bringing a new drug to market in the United States costs roughly $2.6 billion by one calculation, and takes over a decade.[18] And successful regulatory approval is not guaranteed. Most new drugs that enter clinical trials fail; the rate of successful FDA approval is estimated at only 11–14 percent.[19]

For outbreak disease countermeasures, the lack of a clearly defined market exacerbates the costs and risks. Outbreaks, by definition, are sporadic and

[16] WHO, *2018 Annual Review of Diseases Prioritized under the Research and Development Blueprint*, Meeting Report, Geneva, Switzerland, February 6–7, 2018, www.who.int/docs/default-source/blue-print/2018-annual-review-of-diseases-prioritized-under-the-research-and-development-blueprint.pdf (last visited Feb. 5, 2023).

[17] CEPI, Coalition for Epidemic Preparedness Innovations, Preliminary Business Plan 2017–2021 (Washington, DC: CEPI, 2016), 14, 54. https://cepi.net/wp-content/uploads/2019/02/CEPI-Preliminary-Business-Plan-061216_0.pdf (last visited Feb. 5, 2023).

[18] Aaron E. Carroll, *$2.6 Billion to Develop a Drug? New Estimate Makes Questionable Assumptions*, N.Y. Times (Nov. 18, 2014), www.nytimes.com/2014/11/19/upshot/calculating-the-real-costs-of-developing-a-new-drug.html (last visited Feb. 5, 2023).

[19] Katarzyna Smietana, Marcin Siatlowski & Mortin Møller, *Trends in Clinical Success Rates*, 15 Nat. Rev. Drug Discov. 379, at 379–380 (2016); Chi Heem Wong, Kien Wei Siah & Andrew W Lo, *Estimation of Clinical Trial Success Rates and Related Parameters*, 20 Biostatistics, at 273–286 (2019).

unpredictable. It is nearly impossible to know precisely which pathogens will cause health emergencies, or when. And even identifying high-risk pathogens is only a first step as pathogens mutate over time. Pharmaceutical companies also cannot predict the number of doses needed to contain an outbreak, which often is quite small. And low- and middle-income countries are often hit hardest by novel pathogens. Consequently, industry lacks financial incentives to develop products for many novel diseases.

Each stage in the medical countermeasure development process highlights the deficiency of existing market incentives to stimulate innovations. Most drug and vaccine development originates with basic scientific research, usually conducted by government-funded academic researchers.[20] Traditionally, governments fund research for diseases that cause the most illness and death in their populations, such as cancer, diabetes, or cardiovascular disease. This is beginning to change. The United States, for example, has classified Ebola as a bioterrorism threat and "category A priority pathogen." But the NIH has not prioritized other novel pathogens, and thus extant pipelines reflect fewer drug candidates.[21]

The second step in the process is product development, where researchers translate basic scientific findings into a drug or vaccine candidate. This resource- and time-intensive process involves identifying a candidate, optimizing it to lessen unintended interactions, and testing it for toxicity. If successful in animal models, the drug or vaccine undergoes three phases of clinical trials, using increasing numbers of patients, to gather evidence about the candidate's safety and efficacy. Clinical trials are challenging even under the best conditions, but when the study timeline must be compressed to fit within an outbreak, then lengthy regulatory review, dosage shortages, low participation, and poor trial design can cripple a trial's chance of success.[22]

In some cases, a medical countermeasure can gain emergency use authorization (EUA) before completing the entire clinical trial process. For example, in May 2020, the FDA authorized the emergency use of the drug remdesivir to treat COVID-19 patients hospitalized with severe respiratory symptoms.[23]

[20] Christopher J. Elias, Policies and Practices to Advance Global Health Technologies, Report, CSIS, Washington, DC (Apr. 2009), https://csis-website-prod.s3.amazonaws.com/s3fs-public/legacy_files/files/media/csis/pubs/090420_elias_policiespractices.pdf (last visited Feb. 5, 2023).

[21] Coalition for Epidemic Preparedness Innovations, Preliminary Business Plan 2017–2021, CEPI (Nov. 2016), https://cepi.net/wp-content/uploads/2019/02/CEPI-Preliminary-Business-Plan-061216_0.pdf (last visited Feb. 5, 2023).

[22] Theresa Wizemann, Sally Robinson & Robert Giffin, Breakthrough Business Models: Drug Development for Rare and Neglected Diseases and Individualized Therapies (2009).

[23] FDA Approves First Treatment for COVID-19, FDA news release (Oct. 22, 2020), www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19#:~:text=Today%2C%20the%20U.S.%20Food%20and,of%20COVID%2D19%20requiring%20hospitalization (last visited Feb. 5, 2023).

The FDA's decision followed two clinical trials demonstrating efficacy in COVID-19 recovery. The pharmaceutical company Gilead originally developed remdesivir to treat Ebola, but it had been found ineffective for that purpose.

Emergency use authorization can be controversial precisely because phase 3 clinical trials are not always completed. For example, on August 23, the FDA issued an EUA for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients.[24] The EUA coincided with warnings from senior National Institute of Health officials that the data were not sufficient for such authorization.[25]

If a product successfully completes clinical trials, its sponsor must obtain regulatory approval from each country in which the product will be marketed and distributed. Countries usually have their own national regulatory agencies, and the rigor of agency reviews is highly variable. For countermeasures primarily used in lower-income countries, drug sponsors must navigate regulatory regimes that often lack capacity to conduct robust and independent reviews. Thus, sponsors often also seek approval from a more stringent regulatory agency, such as those in the United States, the European Union, or Japan, and prequalification from the WHO, which is frequently viewed by low-income countries as a prerequisite for national approval.

Finally, after receiving regulatory approval, the product must be manufactured at scale and introduced into the country, raising a new set of logistical and operational challenges. Manufacturing capabilities in lower-income countries are often weak. Successful product introduction requires effective distribution channels, ensuring sufficient supply and procurement. Health providers must be made aware of the new product, and, if necessary, trained in its use.

2 OVERCOMING R&D OBSTACLES

Scientific understanding and technologies for developing medical countermeasures have exploded in recent years. Advancements in genetics allow for early pathogen sequencing, helping identify the proteins needed for vaccine design. Two technologies have especially propelled vaccine development: synthetic vaccinology and platform technologies. In synthetic vaccinology, sequencing data are digitally communicated – from scientist to scientist and country to country – without the need for transferring biological samples.

[24] FDA Issues Emergency Use Authorization for Convalescent Plasma as Potential Promising COVID–19 Treatment, Another Achievement in Administration's Fight against Pandemic, FDA (Aug. 23, 2020), www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment (last visited Feb. 5, 2023).

[25] *National Convalescent Plasma EUA Results: Not Sufficient Evidence for Claim that Convalescent Plasma Reduces COVID-19 Death Rate*, Trial Site News (Aug. 15, 2020), www.trialsitenews.com/national-convalescent-plasma-eua-results-not-sufficient-evidence-for-claim-that-convalescent-plasma-reduces-covid-19-death-rate/ (last visited Feb. 5, 2023).

With platform technologies, instead of "one bug, one drug," the idea is to support development of multiple vaccines or drugs with one or more components.[26] As demonstrated by COVID-19 vaccine development, platform technologies can speed up and simplify vaccine production, enabling the rapid development of "plug and play" vaccines where multiple different vaccines can be developed using the same system. Platform technologies can also reduce the need for cold storage, easing the burdens of stockpiling and distribution.

While the science behind developing countermeasures has progressed rapidly, the incentives and regulatory process for translating scientific research into safe and effective products with market approval have lagged behind. The COVID-19 pandemic has compelled investment and regulatory systems for governing R&D to "catch up" to the science, with reforms to overcome many of the barriers in the R&D process – yet challenges remain.

A *Coordinating Research and Development*

The 2014–16 West African Ebola epidemic highlighted major gaps in R&D coordination between stakeholders: confusion and poor organization led to delays in affected countries receiving funds, equipment, medical countermeasures, and personnel.[27] In the wake of the outbreak, global commissions examined the international response and identified the importance of cooperation and coordination.

Coordination of stakeholders' R&D activities helps ensure efficient use of scarce resources, prioritize work on the most worrying diseases and most promising technologies, reduce duplicative activities, and marshal technical expertise. With COVID-19 vaccine development proceeding at record pace, coordination has proven critical on other grounds: both ensuring sufficient global supply of the safest and most efficacious COVID-19 vaccines and equitably distributing those vaccines to the world's population.

In April 2020, WHO launched the Access to COVID-19 Tools (ACT) Accelerator, supported by public and private actors including the European Commission, the Bill and Melinda Gates Foundation, CEPI, Gavi, Global Fund, UNITAID, and the Wellcome Trust.[28] The ACT Accelerator aims to align global efforts for equitable access to new COVID-19 diagnostics, therapeutics, and vaccines. The WHO, given

[26] *Vaccine Platforms: State of the Field and Looming Challenges*, Johns Hopkins Center for Health Security (2019), https://centerforhealthsecurity.org/2019/center-for-health-security-report-reviews-the-promise-and-challenges-of-vaccine-platform-technologies (last visited Feb. 5, 2023).

[27] Lena H. Sun, *Global Response to Ebola Marked by Lack of Coordination and Leadership, Experts Say*, Wash. Post (Sep. 11, 2014), www.washingtonpost.com/national/health-science/global-response-to-ebola-marked-by-lack-of-coordination-and-leadership-experts-say/2014/09/11/35365264-39dc-11e4-8601-97ba88884ffd_story.html (last visited Feb. 5, 2023).

[28] WHO, ACT-Accelerator Update (Jun. 26, 2020), www.who.int/news-room/detail/26-06-2020-act-accelerator-update (last visited Feb. 5, 2023).

its technical expertise and unique legitimacy for global leadership, has developed global policy recommendations on the use of COVID-19 vaccines though its Strategic Advisory Group of Experts (SAGE) on Immunization.

Yet equitable and timely access to COVID-19 vaccines simply could not be achieved without reaching the scale of vaccine production necessary to meet vast global need. For manufacturers, expanding production for vaccines that are still being developed, and may never get approved, comes with enormous financial risk. Many countries and groups of countries, including Canada, China, the United States, and the European Union, addressed this challenge through bilateral agreements with vaccine manufacturers to meet their own COVID-19 needs – a troubling development which coined the term "vaccine nationalism" – the hording of vaccines by governments to meet their populations' needs.[29]

On May 15, 2020, the Trump Administration launched Operation Warp Speed, which had the goal of delivering 300 million COVID-19 vaccine doses across the United States, with initial supplies by January 2021.[30] A key element was to manufacture vaccines at industrial scale while they were simultaneously undergoing clinical trials. Normally, vaccines are not manufactured at scale until after regulatory approval. As only 11–14 percent of countermeasures typically are approved, waiting for approval before large-scale manufacture reduces the possibility of wasted investments.

However, in Operation Warp Speed, the US government took on the financial risk, allowing vaccine developers to expedite production of the most promising vaccine candidates. In July 2020, the US government announced a $2.1 billion deal with vaccine makers Sanofi and GlaxoSmithKline to develop their COVID-19 vaccine candidate and produce 100 million doses by 2021 – bringing the list of US-supported COVID-19 vaccine candidates to six.[31] Operation Warp Speed's overall budget was $10 billion, with $6.5 billion directed toward countermeasure development, and the remainder for NIH research.

Other high-income countries, along with some middle-income ones, have undertaken similar efforts to rapidly develop and produce COVID-19 vaccines. France, Italy, Germany, and the Netherlands formed the Inclusive Vaccine Alliance, with a deal to purchase 400 million doses of AstraZeneca's vaccine for EU member

[29] Rebecca Weintraub, Asaf Bitton & Mark L. Rosenberg, *The Danger of Vaccine Nationalism*, Harv. Bus. L. Rev. (May 22, 2020), https://hbr.org/2020/05/the-danger-of-vaccine-nationalism (last visited Feb. 5, 2023).

[30] Fact Sheet: Explaining Operation Warp Speed, U.S. Department of Health & Human Services (Jun. 16, 2020), www.hhs.gov/about/news/2020/06/16/fact-sheet-explaining-operation-warp-speed.html (last visited Feb. 5, 2023).

[31] GlaxoSmithKline plc, *Sanofi and GSK Selected for Operation Warp Speed to Supply United States Government with 100 Million Doses of COVID-19 Vaccine* (Jul. 31, 2020), www.gsk.com/en-gb/media/press-releases/sanofi-and-gsk-selected-for-operation-warp-speed-to-supply-united-states-government-with-100-million-doses-of-covid-19-vaccine/ (last visited Feb. 5, 2023).

states.[32] The United Kingdom signed its own deals with AstraZeneca and other companies as well. All told, high-income countries had agreements covering 4 billion doses as 2020 drew to a close, while middle-income countries had agreements for close to 3 billion doses, which threatened access of low- and many middle-income countries.[33] Meanwhile, China and Russia were developing their own COVID-19 vaccines, with promises to share them widely, including widespread interest in Latin America, Asia, and the Middle East,[34] The Serum Institute of India produced 50 million doses of the AstraZeneca vaccine even before the United Kingdom and India granted regulatory approval.

Beyond the enormous financial risks governments take by investing in the large-scale production of still unapproved vaccines, this siloed, country-by-country approach is concerning for two major reasons. First, competition among vaccine candidates could lead countries to "panic buy" – creating a bidding war and driving up prices on the global market. Second, given that many vaccine candidates will fail, access to successful candidates may become limited to the few privileged countries that selected them. Lower-income countries, lacking the ability to take financial risks and enter advance supply agreements, would be left especially defenseless.

To avoid this dire outcome, the COVID-19 Vaccine Global Access (COVAX) Facility was assembled by CEPI and Gavi, working under the WHO's leadership.[35] Founded in 2017, CEPI's mission is to engage governments and the commercial sector to improve public health preparedness – which proved critical during COVID-19. Gavi was founded in 2000 to expand childhood vaccine campaigns in the world's poorest countries but has since expanded its charge to procure COVID-19 vaccines globally. The COVAX Facility is a financing and procurement mechanism that pools countries' demand and resources for COVID-19 vaccines. By inviting all countries to join, COVAX takes a collective approach, allowing for a much larger portfolio of vaccine candidates than countries can achieve on their own, thus reducing the risk that countries will fail to secure access to successful vaccines. For manufacturers, it reduces the risks that major production investments could result in no or low demand.

[32] Government of France, *European Initiative for the Covid-19 Vaccine* (Jun. 5, 2020), www.gouvernement.fr/en/european-initiative-for-the-covid-19-vaccine (last visited Feb. 5, 2023).

[33] *COVID-19: Weekly Vaccine Research Update, Launch and Scale Speedometer*, Duke Global Health Innovation Center (Dec. 18, 2020), https://launchandscalefaster.org/COVID-19 (last visited Feb. 5, 2023).

[34] Emily Baumgaertner & Patrick J. McConnell, *Seeking to Expand Their Influence, China and Russia Market Coronavirus Vaccines around the World*, L.A. Times (Oct. 28, 2020), www.latimes.com/world-nation/story/2020-10-28/china-russia-marketing-coronavirus-vaccines-world (last visited Feb. 5, 2023).

[35] COVID-19 Vaccine Global Access (COVAX) Facility (Jun. 11, 2020), www.keionline.org/wp-content/uploads/COVAX-Facility-Preliminary-technical-design-061120-vF.pdf (last visited Feb. 5, 2023).

Costing an estimated $18.1 billion, COVAX aimed to deliver 2 billion doses of safe and effective COVID-19 vaccines, ones that have passed regulatory approval or WHO prequalification, by the end of 2021.[36] Vaccines were to be distributed to all participating countries equally, proportional to population size, initially prioritizing health-care workers and then expanding to cover the most vulnerable 20 percent of every participating country. As of December 2020, 190 countries had agreed to participate in COVAX – though not the United States or Russia. Wealthier nations would self-finance their vaccines from their own public budgets, and partner with ninety-two low- and lower-middle income countries supported through voluntary donations.

Global public–private partnerships, such as CEPI and Gavi, have been highly effective at bringing rapid funding and expertise to thorny health problems such as COVID-19. They have demonstrated the ability to bring governments together to increase the purchasing power of lower-income countries, while also benefitting higher-income countries that can expand their portfolio of vaccine candidates during an outbreak. But still, uncertainty remains whether COVAX will be able to entice higher-income countries to make the political and financial commitment for COVAX to succeed. In rich countries, national leaders poured resources into their own vaccine development and purchasing, taking care of their own citizens first – while also taking up large portions of the global manufacturing capacity, jeopardizing the possibility of low-income nations having access to COVID-19 vaccines.

But the reality must not be ignored: without investments in equitable vaccine distribution, diseases will continue to circulate among poor, unvaccinated populations. Viruses could mutate, gaining virulence and transmissibility, and spread throughout the world, infecting even vaccinated populations. Strategies for financing the development and distribution of outbreak countermeasures are discussed below.

B *Financing Innovative R&D*

Whether R&D is coordinated by the WHO, governments, partnerships, or private entities, its acceleration requires sustainable funding. Traditionally, governments have offered most R&D funding, supplemented by philanthropy and private industry. In 2015, governments funded 63 percent of neglected disease R&D. Philanthropies, mainly the Gates Foundation and the Wellcome Trust, contributed 21 percent of global funding, and industry contributed the remaining 17 percent.[37] In 2015, industry increased Ebola R&D sevenfold over the previous year, becoming

[36] WHO, *More than 150 Countries Engaged in COVID-19 Vaccine Global Access Facility* (Jul. 15, 2020), www.who.int/news-room/detail/15-07-2020-more-than-150-countries-engaged-in-covid-19-vaccine-global-access-facility (last visited Feb. 5, 2023).

[37] Chapman et al., *supra* note 11, at 8, 74.

the second largest funder of Ebola R&D and other African viral hemorrhagic fevers, behind only the NIH.[38]

In 2016, the Commission on a Global Health Risk Framework for the Future recommended a global commitment of an incremental increase of $1 billion per year to accelerate R&D of drugs, vaccines, personal protective equipment, and medical devices.[39] Yet much more is needed. Developing COVID-19 countermeasures has demanded multibillion-dollar investments in R&D, and has stimulated the use of financing mechanisms to secure funding.

Funding and Financing Mechanisms

Funds can be used to stimulate R&D and overcome market failures, but the question remains how best to channel resources to maximize results. "Delinking" R&D costs from the price of health products is an important concept. The current IP system encourages companies to recoup development costs through high prices, which can make drugs and vaccines unaffordable. The IP system also protects companies from competition by providing patents, exclusive licenses, and regulatory exclusivities – driving up the costs of drugs and vaccines even further. This system can cause two major problems: first, companies may simply avoid developing products needed in uncertain or unlucrative markets; and second, high prices can put essential medicines out of reach of the world's poorest.

By delinking R&D costs from product prices, financing mechanisms aim to encourage innovation without prohibitively expensive prices. Delinkage includes mechanisms to offset development costs through upfront payments or back-end rewards, or through the strategic softening of intellectual property protections. Governments and partnerships relied on these mechanisms to stimulate the development of COVID-19 vaccines, and ultimately ensured their affordability.

Offsetting R&D Costs: Push and Pull Mechanisms

Financing to offset development costs can either provide funding upfront (called a "push") or offer a financial reward once a product has been developed (called a "pull").[40]

Push mechanisms include up-front payments such as grants and innovation funds and are highly effective in spurring R&D for neglected diseases. In 2016, for example, the United States Agency for International Development (USAID) issued a challenge called, "Combating Zika and Future Threats." Parties from academia and industry submitted proposals to combat Zika, and USAID awarded $15 million

[38] *Id.*, at 68.

[39] Commission on Global Health Framework for the Future, Neglected Dimension of Global Security: A Framework to Counter Infectious Disease Crises (2016), 7.

[40] Robert Hecht, Paul Wilson & Amrita Palriwala, *Improving Health R&D Financing for Developing Countries: A Menu of Innovative Policy Options*, 28 (4) Health Aff. (Millwood) at 974–985 (2009).

in grants for projects that ranged from insecticide-treated sandals to mosquitos infected with bacteria that prevent the spread of disease to humans.[41]

Although push financing mechanisms are popular, funding is not contingent upon the recipient successfully furthering R&D. "Pull" mechanisms, alternatively, reward successful innovation with financing. Pull mechanisms come in a variety of forms, including prizes, transferable vouchers, and advance market commitments. For example, the FDA Priority Review Voucher program awards a transferable voucher to the sponsor of a new drug to treat delineated tropical diseases, such as Ebola, Zika, and Lassa Fever. The holder of the voucher can redeem it for expedited review of a new drug or can sell it to another company. For example, a voucher awarded to Knight Therapeutics in 2014 for its leishmaniasis drug was sold to Gilead Sciences for $125 million. Gilead used the voucher for accelerated review of its HIV drug Odefsey.[42] The race for the COVID-19 vaccine was financed through both push and pull mechanisms. As part of Operation Warp Speed in the United States, the Biomedical Advanced Research and Medical Authority (BARDA) had a budget of $6.5 billion to "push" the development, manufacture, and distribution of promising COVID-19 vaccine candidates.[43] BARDA formed agreements to provide millions and even billions to vaccine companies (including Pfizer, AstraZeneca, Moderna, Johnson & Johnson, Novavax, Sanofi, and GlaxoSmithKline), to cover the costs of testing, commercialization, and manufacture. BARDA also partnered with manufacturers and producers of supplies such as vials, syringes, and plastic containers. By securing the financing up-front, companies can focus on rapid vaccine development without incurring much financial risk.

Similar to BARDA, CEPI's role in the COVAX Facility was to push the development of COVID-19 vaccines by signing contracts with developers of promising candidates to help fund research, clinical trials, and manufacturing capacity.[44] CEPI initiated partnerships with nine vaccine companies to finance the development of their COVID-19 vaccine candidates.

Concurrent to CEPI's push mechanisms within COVAX, Gavi employed a pull mechanism: advance market commitments (AMC).[45] The goal of AMCs is to

[41] USAID Invests over $15 Million to Accelerate Development and Deployment of 21 Innovations to Combat the Spread of Zika, USAID (Aug. 10, 2016), https://2012-2017.usaid.gov/news-information/press-releases/aug-10-2016-usaid-announces-initial-results-grand-challenge-combat-zika (last visited Feb. 5, 2023).

[42] Alexander Gaffney, Michael Mezher & Zachary Brennan, *Regulatory Explainer: Everything You Need to Know about FDA's Priority Review Vouchers*, Reg. Aff. Professionals Soc'y (Feb. 25, 2020), www.raps.org/news-and-articles/news-articles/2017/12/regulatory-explainer-everything-you-need-to-know (last visited Feb. 5, 2023).

[43] HHS Fact Sheet, *supra* note 30.

[44] CEPI, *COVAX: Ensuring Fair Allocation of a COVID-19 Vaccine* (Jun. 26, 2020), https://cepi.net/news_cepi/covax-ensuring-fair-allocation-of-a-covid-19-vaccine/ (last visited Feb. 5, 2023).

[45] GAVI, *Gavi Launches Innovative Financing Mechanism for Access to COVID-19 Vaccines* (Jun. 4, 2020), www.gavi.org/news/media-room/gavi-launches-innovative-financing-mechanism-access-covid-19-vaccines (last visited Feb. 5, 2023).

counter market forces that push down drug prices by ensuring a stable market for a product once it is developed. Many factors can drive down drug prices, including the absence of a lucrative market in low-income countries, and the practice of "bulk purchasing" vaccines. Under bulk purchases, health ministries purchase most vaccines, using their buying power to negotiate lower prices. From the country's perspective, this is a wise use of limited resources, but by driving vaccine company profits even lower, bulk purchasing can disincentivize vaccine development targeted at low-income countries.[46] With AMCs, a purchaser promises vaccine developers that it will buy a certain number of doses, at a predetermined price, if the developers can clear the necessary regulatory hurdles.

In 2010, Gavi successfully piloted an AMC for pneumococcal vaccines.[47] Donors committed $1.5 billion to the World Bank to guarantee the price of pneumococcal vaccines once developed, and suppliers agreed to provide vaccine doses at a predetermined price. In return, each manufacturer received its proportional share of the committed funds.[48] This financing program has been credited with an estimated 225 million children vaccinated against the virus across sixty low- and low–middle-income countries within the decade after the program was launched.[49]

Within COVAX, Gavi worked with participating countries and donors to assemble the funding to enter into AMCs with CEPI's COVID-19 vaccine development partners.[50] As with the pneumococcal vaccine program, the AMCs sought to help ensure that the funding of vaccines for low-income countries remains stable, thus incentivizing their development and manufacture. Gavi estimated that $2 billion was needed to provide 1 billion doses to ninety-two low-income countries through AMCs. By the end of October 2020, Gavi had successfully raised these funds from participating countries (including Italy, the United Kingdom, Canada, and Norway), as well as the private sector, yet as 2020 drew to a close, the COVAX AMC still needed nearly $5 billion, while more than $2 billion was still required for country readiness and late-stage clinical trials.[51]

[46] Making Markets for Vaccines: Ideas to Action, Center for Global Development, Report, Washington, DC, 14 (2005), www.cgdev.org/sites/default/files/archive/doc/books/vaccine/MakingMarkets-complete.pdf (last visited Feb. 5, 2023).

[47] GAVI, *Positive Impact of Advance Market Commitment Highlighted in Report* (Feb. 26, 2016), www.gavi.org/library/news/press-releases/2016/positive-impact-of-advance-market-commitment-highlighted-in-report/ (last visited Feb. 5, 2023).

[48] GAVI, *How the Pneumococcal AMC Works* (updated Feb. 28, 2020) www.gavi.org/investing-gavi/innovative-financing/pneumococcal-amc/how-it-works (last visited Feb. 5, 2023).

[49] Allie Nawrat, *Access to Covid-19 Vaccines: Deep Dive into Gavi's COVAX AMC*, Pharmaceutical Tech. (Jul. 27, 2020), www.pharmaceutical-technology.com/features/gavi-covax-amc-covid-19/ (last visited Feb. 5, 2023).

[50] *Gavi Launches Innovative Financing Mechanism*, *supra* note 45.

[51] GAVI, *COVAX Announces Additional Deals to Access Promising COVID-19 Vaccine Candidates; Plans Global Rollout Starting Q1 2021* (Dec. 18, 2020), www.gavi.org/news/media-room/covax-announces-additional-deals-access-promising-covid-19-vaccine-candidates-plans (last visited Feb. 5, 2023).

As demonstrated by COVAX, push and pull mechanisms can work in concert: initial financing agreements reduce the risks of product development, while purchase agreements contingent on product approval help assure a stable market in low-income countries.

Decreasing R&D Costs: More Flexible IP Protections

The push and pull mechanisms discussed above all involved funding to offset R&D costs, lessening the need for companies to set high drug or vaccine prices to recoup costs, while leaving IP protections intact. But problems remain. Successful COVID-19 vaccines developed in rich countries, outside of COVAX's AMCs or other agreement, could be unaffordable for poorer populations in all other countries. Reducing IP protections in defined scenarios, such as patent pools, licensing agreements, and open-source approaches to R&D, is thus essential to global access.

Patents increase drug prices by providing companies an exclusive right to use, make, or sell their inventions for a defined period of time, blocking competition for the length of the patent period. And without competition, the patent holder can charge high prices even for essential drugs.

Patent pools aim to lower IP barriers to competition and affordable pricing. The Medicines Patent Pool is an existing United Nations-backed entity that pools patents for HIV, hepatitis C, and tuberculosis medicines. During the COVID-19 pandemic, the Pool's scope was expanded to cover COVID-related medical products. Under the Pool's model, patent holders voluntarily license patented products to the Pool, which then sublicenses them to generic manufacturers. The voluntary licenses are generally restricted geographically to low- and middle-income countries so that the patent holder retains exclusive rights in lucrative markets. Royalties (albeit low) are paid to patent holders upon sale of the resulting products.

In May 2020, the WHO and Costa Rica launched the Solidarity Call to Action as a complement to the WHO's ACT Accelerator.[52] The Solidarity Call asked countries to ensure that all COVID-19 publicly funded and donor-funded research outcomes are made affordable, accessible, and available on a global scale through provisions in funding agreements (for example, non-exclusive voluntary licensing), as well as national legal and policy measures to lower barriers such as intellectual property rights. In an "open source" approach, the Solidarity Call encourages research outcomes to be published with no restrictions, and collaborative efforts are taken in pre-competitive drug discovery. By December 2020, about forty countries had endorsed the Solidarity Call, but notably the United States, China, the United Kingdom, and other countries with high vaccine development capacity had not.[53]

[52] WHO, *Making the Response to COVID-19 a Public Common Good: Solidarity Call to Action* (May 29, 2020), www.who.int/initiatives/covid-19-technology-access-pool/solidarity-call-to-action (last visited Feb. 5, 2023).

[53] WHO, *Endorsements of the Solidarity Call to Action* (Dec. 2020), www.who.int/initiatives/covid-19-technology-access-pool/endorsements-of-the-solidarity-call-to-action#:~:text=

Not surprisingly, the pharmaceutical industry strongly opposed the Solidarity Call.[54] Companies that are investing billions in developing COVID-19 countermeasures could lose incentive to innovate if they perceive that their intellectual property rights could be jeopardized. Industry has similarly opposed countries' efforts to lay the legal groundwork for issuing compulsory licensing agreements for COVID-19 countermeasures if necessary. Under compulsory licensing, which the 2001 Doha Declaration allows under extraordinary circumstances to protect public health, governments can grant a license to a public agency or generic drug maker to copy a patented medicine without the patent owners' consent.[55]

To avoid this, companies have voluntarily entered into licensing agreements to supply COVID-19 countermeasures to low-income countries. For example, AstraZeneca reached an agreement with the Serum Institute of India to supply 1 billion doses of its COVID-19 vaccine candidate, once approved, to low- and middle-income countries including India.[56]

The coming together of individual countries and industry stakeholders to overcome IP barriers is important. And yet, as long as these efforts remain disjointed, equitable access to outbreak countermeasures among the world's poorest remains at stake. Global solidarity in efforts like the Medicines Patent Pool and Solidarity Call to Action may be the only true solution to ensuring affordable countermeasures universally.

C *Facilitating Product Approval*

Even with good coordination and adequate funding, promising medical countermeasures often fail during clinical trials or are delayed due to the product approval process. Under an accelerated timeline, the Ebola vaccine did not even receive full regulatory approval until five years after it entered clinical testing. Clinical trials and regulatory approval are both vital to ensure safety and effectiveness, and yet research and regulatory processes could be far more efficient.

Resolving Clinical Trial Design Conflicts

The challenges of designing and conducting clinical trials for outbreak diseases slow or stop promising products from advancing. Clinical research can often only be

Endorsements%20of%20the%20%22Solidarity%20call,health%20technology%20related%20access%20work (last visited Feb. 5, 2023).

[54] Ed Silverman, *Pharma Leaders Shoot Down WHO Voluntary Pool for Patent Rights on Covid-19 Products*, STAT NEWS (May 28, 2020), www.statnews.com/pharmalot/2020/05/28/who-voluntary-pool-patents-pfizer/ (last visited Feb. 5, 2023).

[55] WTO, Declaration on the TRIPS Agreement and Public Health, DOHA, WTO Ministerial Conference on Trips Agreement: WT/MIN(01)/DEC/2 (adopted on November 14, 2001), www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm (last visited Feb. 5, 2023).

[56] AstraZeneca, *AstraZeneca Takes Next Steps towards Broad and Equitable Access to Oxford University's Potential COVID-19 Vaccine* (Jun. 4, 2020), www.astrazeneca.com/media-centre/press-releases/2020/astrazeneca-takes-next-steps-towards-broad-and-equitable-access-to-oxford-universitys-covid-19-vaccine.html#! (last visited Feb. 5, 2023).

conducted during a major outbreak, when there are sufficient numbers of patients to support well-designed trials. In fact, the WHO Ethics Working Group has stated that only by conducting clinical trials in outbreak settings could clinicians be assured that scarce resources were being put to their best use.[57] Developing a clinical trial for implementation during an epidemic is especially complex. Authorities must determine which products are sufficiently promising to be tested during the compressed timeline of an outbreak.[58] Researchers must design the trials considering factors such as relevant clinical end points, the study size, the effect of herd immunity, and whether to include vulnerable populations like pregnant women and children. Prior to approval, products typically undergo three phases of clinical testing, a process that can take a decade.

Development of the Ebola vaccine from 2014 to 2019 yielded several lessons on expediting vaccine development.[59] Researchers were given more flexibility in conducting clinical trials. Regulatory agencies from the United States, Canada, and Europe collaborated closely with each other and with National Regulatory Authorities of the impacted West African countries, sharing information on vaccine candidates and testing protocols.[60] Regulatory agencies also consulted with researchers on the safety and efficacy thresholds required for vaccine approval.

These lessons facilitated COVID-19 vaccine development: researchers were authorized to conduct combined phase 1/2 and phase 2/3 trials, simultaneously testing safety and efficacy to cut months off the clinical trial process.[61] Companies such as Pfizer were authorized to design trials where multiple vaccine candidates were tested in parallel.[62] Both the WHO and FDA advised on clinical trial study design, outlining that vaccines must prevent infections or reduce the severity of COVID-19 cases by at least 50 percent to be approved. The FDA's Fast Track designation allowed drug sponsors to interact with the FDA review team about clinical trial concerns such as study design, safety data, dosing, and biomarker use. In the FDA's guidance for COVID-19 Fast Track review, the agency emphasized the need to include diverse populations in clinical testing, using sufficiently large

[57] Emily R. Busta et al., Integrating Clinical Research into Epidemic Response: The Ebola Experience 40 (2017).

[58] *Id.*, at 46.

[59] Joyanthi Wolf et al., *Applying Lessons from the Ebola Vaccine Experience for SARS-CoV-2 and Other Epidemic Pathogens*, 5 NPJ Vaccines 51 (2020).

[60] Andrew Joseph, *"A Huge Experiment": How the World Made So Much Progress on a Covid-19 Vaccine So Fast*, STAT News (Jul. 30, 2020), www.statnews.com/2020/07/30/a-huge-experiment-how-the-world-made-so-much-progress-on-a-covid-19-vaccine-so-fast/ (last visited Feb. 5, 2023).

[61] *Id.*

[62] Knvul Sheikh, *Pfizer Begins Human Trials of Possible Coronavirus Vaccine*, N.Y. Times (May 5, 2020), www.nytimes.com/2020/05/05/health/pfizer-vaccine-coronavirus.html (last visited Feb. 5, 2023).

population sizes to detect safety or efficacy issues, and conducting post-market studies to continue evaluating safety and efficacy even after approval.[63]

The 2014–2016 Ebola epidemic also revealed an R&D pitfall: stakeholders had no clear agreement on what and how to share epidemiological and research data. This slowed experts' understanding of the outbreak and hindered the response.[64] The lack of a sharing platform led to post-outbreak calls to develop better incentives and mechanisms for sharing data. It also incentivized the WHO's ACT Accelerator for sharing COVID-19 data, as discussed previously. But sharing data remains difficult. Intellectual property and ownership claims arise, such as who owns submitted data, and who has the right to access and benefit from their eventual commercialization. Questions arise on patients' privacy and consent, whose personal information should be protected when their data are shared. And researchers bear uncertainty about their rights to publish previously submitted data, and potential reputational damage if early research findings are later undermined. Despite these concerns, it remains essential that information on drug and vaccine efficacy, as well as adverse events, are disseminated quickly and openly to ensure rapid development of safe and effective outbreak countermeasures.

Steps taken before an outbreak occurs can facilitate the rapid development of countermeasures. It is important, for example, to identify promising products during inter-epidemic periods. Identification by the WHO of technical specifications for drugs and vaccines for priority pathogens can reduce the time spent evaluating products. And work by CEPI to advance vaccine candidates and platform technologies should make identifying products for clinical trials simpler.

In addition, using inter-epidemic periods to manage regulatory and administrative tasks can facilitate a more rapid response. For example, developing generic clinical trial designs for likely outbreak scenarios and getting buy-in from stakeholders such as ethics boards and communities will provide affected parties with an advanced starting point for discussions when an outbreak occurs. Similarly, protocols and platforms for sharing outbreak and countermeasure data should be established far in advance of an outbreak, with regulatory guidelines on protecting intellectual property and patients' privacy.

Reforming Product Registration

Once a product is developed, regulatory approvals are needed prior to marketing a drug or vaccine in a country.[65] Products must be registered with a country's national

[63] FDA, Coronavirus (COVID-19) Update: FDA Takes Action to Help Facilitate Timely Development of Safe, Effective COVID-19 Vaccines (Jun. 30, 2020), www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-action-help-facilitate-timely-development-safe-effective-covid (last visited Feb. 5, 2023).

[64] Suerie Moon et al., *Post Ebola Reforms: Ample Analysis, Inadequate Action*, BMJ (Jan. 23, 2017).

[65] Vincent Ahonkhai et al., *Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries: A Case for Change and a Framework for Optimized Product Market Authorization*, PLoS ONE (Nov. 16, 2016).

regulatory agency before they may be sold in the country, ensuring that the products are safe, effective, and meet quality manufacturing standards. Regulatory hurdles can delay the time for products, which are typically developed in higher-income countries, to be distributed in the lower-income countries where they are often needed most.

Products registered in low- and middle-income countries tend to follow a three-step registration process. First, products are registered in the country where they are manufactured. This initial registration often occurs under "stringent regulatory authority," adhering to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH is a collaboration since 1990 between the United States, the European Union, and Japan to harmonize the scientific and technical aspects of drug registration. An increasing number of generic products, however, are first registered by other national regulatory authorities, such as those of India and China.[66]

After initial product registration, the manufacturer can apply to the WHO for prequalification, typically a prerequisite for international aid agencies, such as Gavi, UNICEF, or the Global Fund, to purchase a product for distribution. For example, WHO prequalification was a prerequisite for COVID-19 vaccine developers participating in COVAX's AMCs.[67] The WHO assesses the product's performance, its risk-to-benefit ratio for the intended population, and whether the product is suitable for the proposed use.[68] Lastly, the product is registered with the national regulatory agencies in the low- to middle-income countries where the product will be sold. These authorities work to ensure the safety, efficacy, and quality of the products as applied to the health needs of their citizens.

A 2016 study on product registration in Sub-Saharan Africa found that the time between a product's first regulatory submission and its approval ranged from four to seven years.[69] This lag – where the drug has been approved by a stringent regulatory authority but is not accessible to vulnerable populations in low-income countries – has led to calls for reform.

Proposed reforms to improve efficiency can enhance both the clinical trial and product approval processes. Agencies can avoid duplicative review by leveraging stringent regulatory assessments. Instead of repeating steps, such as inspections of manufacturing facilities, subsequent assessments could focus on activities that fill key gaps. Eliminating duplication could shorten registration time. Countries can also standardize registration requirements among regional or global partners. For

[66] *Id.*

[67] *COVID-19 Vaccine Global Access, Preliminary Technical Design*, Discussion Document, FACILITY (Jun. 11, 2020), www.keionline.org/wp-content/uploads/COVAX-Facility-Preliminary-technical-design-061120-vF.pdf (last visited Feb. 5, 2023).

[68] Ahonkhai et al., *supra* note 65.

[69] *Id.*

example, technical registration requirements differ among African countries, but efforts to develop uniform standards are occurring. In 2012, regulatory agencies in Burundi, Kenya, Rwanda, Tanzania, Uganda, and Zanzibar launched the African Medicine Regulatory Harmonization program, which strives to encourage regional collaboration and harmonization of regulatory standards.[70]

Just as with clinical testing of outbreak countermeasures, costly delays could be avoided if efforts to reform the product registration process are initiated well ahead of an outbreak.

Safety and Ethical Considerations

Reforms to facilitate the testing and approval of outbreak countermeasures could provide drugs and vaccines to at-risk populations sooner – saving countless lives during future epidemics. In some cases, however, expediting countermeasure development implicates safety and ethical considerations that, if ignored, could result in harm to individuals and societies, and destroy trust between authorities, researchers, and communities. Concerns about cutting ethical or scientific corners are especially acute when there is political pressure to bring drugs and vaccines to the market before completion of clinical trials.

The Declaration of Helsinki requires independent ethics review of human participant research. Even in a health emergency, ethical values are vital.[71] At its core, a clinical trial must have sufficient scientific and social value to justify its risks and burdens, and be designed to create quality data to guide regulatory agencies and clinicians. Respect for the participants and community is another core requirement, including participants' rights to informed consent and privacy. Communities should be meaningfully engaged, respecting values, cultures, and traditions, with host countries and local researchers treated as equal partners. Trials should be conducted to ensure that benefits and burdens are distributed equitably. Vulnerable populations should be identified and protected. Once the trial is complete, the community and participants should be informed of the trial results, and have access to successful medical countermeasures.

Even with seemingly straightforward ethics principles, ethically appropriate decisions can be complicated, especially during health emergencies. In some settings, trials might exclude pregnant women and children to avoid health risks. But in other settings, such as when pregnant women are especially vulnerable to a disease like Zika, it may be preferable to include them in clinical trials. Early phase 3 clinical

[70] *Id.*

[71] Article I, World Medical Association, Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964), www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/#:~:text=In%20medical%20research%20involving%20human%20subjects%20capable%20of%20giving%20informed,risks%20of%20the%20study%20and (last visited Feb. 5, 2023).

trials of COVID-19 vaccines, for example, excluded children, thus creating uncertainty as to the vaccines' safety and effectiveness in this population. The policy implications are huge, as it took longer to determine whether children could be vaccinated to enable schools to safely open.

During the 2014 West African Ebola outbreak, an ethical debate raged on the use of randomized controlled trials (RCTs), typically the "gold standard" for clinical trials, for Ebola vaccine candidates.[72] In most RCTs, one group receives an experimental intervention while the other receives a placebo or the conventional care. While RCTs may be the fastest way to generate high-quality data about efficacy and safety, RCTs are not ethical when conventional care means a high probability of death, as with Ebola.[73] Withholding promising interventions under these circumstances also creates distrust and animosity among communities and researchers. For these reasons, a number of leading voices argued against RCTs in the context of the deadly Ebola epidemic.[74] A US National Academies of Sciences committee tasked with reviewing the Ebola vaccine clinical trials acknowledged that uncontrolled trials may be warranted under certain circumstances, such as the unavailability of another treatment as a control, and certainty that patients who don't receive an intervention will have a poor prognosis.[75]

As recognized in the National Academies of Sciences report, the safety and ethics considerations behind clinical trials are highly contextual to the condition being studied. Consider vaccine development for COVID-19, a disease with a far lower death rate than Ebola. As the "race for the vaccine" progressed, many scientists voiced concerns that skipping steps to vaccinate more persons sooner could do more harm than good. In 2017, a dengue vaccine was pulled from the market in the Philippines after the understudied vaccine was attributed with causing severe cases of dengue.[76]

Similar outcomes could have resulted from COVID-19 vaccines being hurried to the markets. In June 2020, China approved the use of an experimental vaccine, manufactured by the company CanSino, for the country's military. Phase 1 and 2 trials of CanSino's vaccine had demonstrated largely mild adverse reactions in some patients, though 9 percent of overall patients had severe side effects that "prevented activity."[77] In August 2020, Russia's Ministry of Health approved a COVID-19 vaccine that had been tested on just seventy-six people by the Gamaleya Research

[72] Busta et al., *supra* note 57, at 75.
[73] Jon Cohen & Kai Kupferschmidt, *Ebola Vaccine Trails Raise Ethical Issues*, Science (Oct. 17, 2014), at 289–290, www.science.org/doi/full/10.1126/science.346.6207.289 (last visited Feb. 5, 2023).
[74] Clement Adebamowo et al., *Randomised Controlled Trials for Ebola: Practical and Ethical Issues*, The Lancet (Oct. 13, 2014), at 1423–1424.
[75] Busta et al., *supra* note 57, at 64.
[76] Annelies Wilder-Smith, Stefan Flasche & Peter G. Smith, *Vaccine-Attributable Severe Dengue in the Philippines*, The Lancet (2019), at 2151–2152.
[77] *Id.*

Institute.[78] The vaccine had undergone phase 1 testing on volunteers from Russia's military – whose ability to render informed consent is highly questionable. Dubbed "Spuknik V," scientists around the world denounced the approval as premature and inappropriate, as the vaccine had yet to be proven safe and effective for a large group of people.[79]

In the United States, the FDA by law can only approve vaccine candidates that have been proven safe and effective in phase 3 trials. Vaccine candidates in phase 3 enroll tens of thousands of people with diverse health circumstances from across the country, which is critical to determining safety and efficacy in a real-world setting.[80] If the FDA determines that a vaccine is safe and effective, the agency can approve the vaccine through an emergency-use authorization prior to the trial's completion. Yet the US regulatory system was put under pressure by the Trump Administration and Operation Warp Speed. Many experts worried that the FDA would succumb to the pressure to approve a COVID-19 vaccine prior to the presidential election in November 2020.[81] Unlike in Russia, the FDA has an independent advisory committee that reviews approval applications. Still, concerns arose when the FDA issued and later revoked emergency approval for hydroxychloroquine to treat COVID-19 patients. The drug, which had been praised by President Trump, was found ineffective at treating COVID-19, and associated with severely adverse cardiac events.[82] Fortunately, the FDA performed admirably in granting emergency use authorization for COVID-19 vaccines. The agency used its scientific advisory committee, disclosed all data transparently, and granted authorization only after all the processes were completed.

Unproven countermeasures come with enormous safety risks, underscoring the need for fully informed consent for participation in clinical trials. Candidates for COVID-19 countermeasures could cause serious adverse reactions, or even make COVID-19 infections more lethal – leading to thousands of needless hospitalizations and deaths. Aside from these immediate harms, approving unproven countermeasures contributes to distrust of science when they are found unsafe or ineffective at

[78] Jon Cohen, *Russia's Approval of a COVID-19 Vaccine Is Less than Meets the Press Release*, Science (Aug. 11, 2020), www.science.org/content/article/russia-s-approval-covid-19-vaccine-less-meets-press-release (last visited Feb. 5, 2023).

[79] Lawrence Gostin, *Russia's Covid-19 Vaccine Breaches Crucial Scientific and Ethical International Standards*, Moscow Times (Aug. 12, 2020), www.themoscowtimes.com/2020/08/12/russias-covid-19-vaccine-breaches-crucial-scientific-and-ethical-international-standards-a71121 (last visited Feb. 5, 2023).

[80] NIH, *Phase 3 Clinical Trial of Investigational Vaccine for COVID-19 Begins* (Jul. 27, 2020), www.nih.gov/news-events/news-releases/phase-3-clinical-trial-investigational-vaccine-covid-19-begins (last visited Feb. 5, 2023).

[81] Cohen, *supra* note 78.

[82] FDA, *Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine* (Jun. 15, 2020), www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and (last visited Feb. 5, 2023).

preventing disease in a population. Vaccine hesitancy has been a major challenge globally, resulting in a resurgence of measles and other childhood diseases.[83] In a poll from August 2020, one-third of Americans, and over 40 percent of non-white Americans, said they would not get a COVID-19 vaccine.[84] Such high refusals jeopardize immunity, particularly among populations that have suffered a history of medical inequities. A rigorous scientific process for putting new countermeasures on the market is absolutely critical to countering public distrust of science and political leaders.

Rigorous scientific process must go hand in hand with transparency from decision-makers at every stage of the R&D process. Transparency helps garner public trust and achieve cooperation with public health recommendations. Operation Warp Speed was criticized when scientists involved with the program disclosed they were excluded from decisions to select the vaccine candidates to receive funding for rapid testing and manufacture.[85] In a letter signed by over 400 experts in infectious diseases, vaccines, and other medical specialties, the group implored FDA Commissioner Stephen Hahn to disclose the agency's deliberations on whether to approve a COVID-19 vaccine.[86] Access to this information would have enabled scientists and health professionals to independently assess and, ideally, promote a safe and effective COVID-19 vaccine to the American people. On a global scale, the WHO must be provided full access to robust information on countermeasure approval decisions. With trusted and informed "gatekeepers" in place from multiple governance realms, the world can maximize the use of safe and effective countermeasures, with a defense against potentially harmful ones.

D *Enabling Scientific Innovation*

Modern medical tools are essential to combat ongoing threats to global health. Technology offers a way to stock our medical war chest before the next outbreak, epidemic, or pandemic. Vaccines are among the greatest public health achievements in the modern era. Discovering and deploying vaccines against outbreak diseases would be a sound investment in national and global security. Therapeutic agents such as drugs and biologics would lessen suffering and death worldwide. Improvements in diagnostic devices, surveillance, and data-sharing platforms could

[83] Olivia Benecke & Sarah Elizabeth DeYoung, *Anti-Vaccine Decision-Making and Measles Resurgence in the United States*, 6 Global Pediatric Health 2333794X19862949 (2019).

[84] Shannon Mullen O'Keefe, *One in Three Americans Would Not Get COVID-19 Vaccine*, Gallup (Aug. 7, 2020), https://news.gallup.com/poll/317018/one-three-americans-not-covid-vaccine.aspx (last visited Feb. 5, 2023).

[85] Jon Cohen, *Top U.S. Scientists Left Out of White House Selection of COVID-19 Vaccine Short List*, Science (Jun. 4, 2020), www.science.org/content/article/top-us-scientists-left-out-white-house-selection-covid-19-vaccine-shortlist (last visited Feb. 5, 2023).

[86] CSPI, Letter to FDA (Aug. 5, 2020), https://cspinet.org/sites/default/files/COVID_Vaccine_Letter_to_FDA_8.5.2020.pdf (last visited Feb. 5, 2023).

enable faster and more efficient detection and response to outbreak pathogens and reduce mortality and morbidity.

Science has the potential for major innovation, often our last defense against catastrophic consequences of pandemic disease. But the financing, law, and ethics must be in place – not just when an outbreak strikes, but more importantly during periods of calm. Lurching from complacency to crisis, and back, will never reduce global vulnerabilities. Collectively, policies and processes that support all the building blocks of research and development can save millions of lives. It is wise to remember that there is an ongoing struggle between pathogens with vast power to mutate and to kill, and science with its capacity to prevent and treat disease. For science to prevail over Mother Nature, we need to invest and prepare, building scientific and manufacturing capacity well before the next pandemic strikes.