# Building the firetruck after the fire: Analyzing the US COVID-19 response and its implications for the future

### Key Takeaways

- Novel pathogen outbreaks and pandemics are likely to continue to increase
- Clinical development pathways need to focus on antiviral libraries and pan-viral vaccines pre-outbreak, and accurate diagnostics during an outbreak
- However, there is a misalignment between public and private incentives that make proactive efforts directed at future outbreaks difficult to manage
- Public-private partnerships, such as CEPI and ACTIV, represent a solution to this misalignment by balancing public and private interests
- Though strategies such as clinical development streamlining and public-private partnerships can increase the speed of response, this speed must be balanced with safety

**Michael Osterholm, director of the Center for Infectious Disease Research and Policy, compared pandemic response to a fire, saying "imagine if we had to go out and buy a firetruck when the 911 call came in."[1] In the case of a fire, this idea seems foolish or even dangerous. However, in the context of COVID-19, reactivity has defined the approach, and the world has struggled to catch up to the rapidly spreading virus.**

**The events from January to the present highlight the gaps and success factors in our preparation to combat new and emerging diseases. By analyzing the response to COVID-19, we can derive learnings on how to respond to the next novel pathogen. In this article, we argue that new pandemics will continue to emerge in the near future. We then discuss three aspects of the COVID-19 response and how these should inform future responses: diagnostics, repurposed therapies, and vaccines. Finally, we characterize the current misalignment between the need for an effective response and the structural barriers that hinder it and suggest that public/private partnerships represent a solution moving forward.**

## New diseases with pandemic potential will continue to arise

COVID-19 is likely not an anomaly. Since 1980, both the rate of infectious disease outbreaks and the diversity of emerging diseases has been steadily increasing, suggesting that novel and deadly diseases will continue to emerge at an increasing pace.[2] Global warming, urbanization, and globalization are changing the global disease composition and burden:[3]

- **Global warming** has increased vector and bacteria habitat size and amplified catastrophes that overwhelm

sanitation and health infrastructure. This leads to a greater geographic spread of disease and reduced capacity to respond to outbreaks
- **Urbanization** has decreased the habitat size for animals, making human / animal interfacing more frequent. This increases the rate of spillover events that result in animal diseases being passed to humans
- **Globalization** has increased rates of travel and migration. This accelerates the exposure of naïve populations to new diseases

As new pandemic threats will continue to emerge, it is important to take a critical eye to the events of the last six months, particularly in the US, to understand how events unfolded and what key learnings can be derived for future outbreaks.

## There are three key aspects of clinical development that need to be prioritized in future outbreaks

When responding to a novel infectious disease (ID) outbreak, all health care responses are essential. However, three key categories should be prioritized for future outbreaks: diagnostics, repurposed therapies, and pan-viral vaccines.

**DIAGNOSTICS** Diagnostics are key in any ID outbreak. They are used to map the spread, decide public health interventions, allocate resources, and build scientific understanding. Therefore, diagnostics should be the first focus in responding to any pandemic. Had diagnostics been prioritized initially in the COVID-19 pandemic, the outcomes we see today may have been vastly different. Examining the series of events surrounding US diagnostics demonstrates how future outbreak response needs to be handled.

Obstacles in initial diagnostic testing in the United States were threefold:

- Initially, in early February, the only diagnostic approved was the CDC's test. This test was ineffective, containing a faulty reagent, and improperly scaled, leaving labs around the country with insufficient supplies to run testing.[4]
- The FDA limited the ability for Laboratory Developed Tests (LDTs) to be developed against COVID-19 by not allowing for "enforcement discretion", meaning that testing had to be approved by the agency.[5]
- What emerged from this delay in establishing proper diagnostics, was a "lost month" of pandemic response, setting the US back in its efforts to track and contain COVID-19.[6,7,8,9] Once the FDA gained authority to issue Emergency Use Authorization (EUA), companies were able to distribute tests pre-approval and labs could produce LDTs.[10]

However, even when labs were finally able to respond, technical issues emerged for both serological and diagnostic testing, including:

- In mid-March, the FDA issued a guidance allowing serological (antibody) tests to launch without review, which led to patients receiving results with unknown or unverified specificity and sensitivity.[11,12,13] By the time the FDA brought serological testing under their domain, patients were already using these tests to make important and possibly dangerous decisions based on a potential false positive.[14]
- Due to a lack of FDA standards and guidance, diagnostics companies were able to produce assays of varying limits of detection.[15,16] These created inconsistency in the testing landscape, subjecting patients to high rates of false positives and negatives

**What should be done differently next time?** Each of these hiccups in diagnostics have delayed and misinformed the COVID-19 response. For the next disease that emerges, the FDA needs to better coordinate with public agencies and private companies, streamline EUA procedures for testing, and implement specificity and sensitivity standards for kits to be approved and marketed. In future pandemics, case tracking, testing, and monitoring need to be the highest priority in the initial pandemic response; without these key factors, public trust in testing can erode, making the pandemic even more difficult to characterize and control.

**REPURPOSED THERAPIES** Repurposed therapies are key during a novel outbreak because of how rapidly they can become available; due to previous trials demonstrating safety and tolerability, repurposed therapies can be launched directly into later stage trials.[17] This can accelerate time to approval and generate necessary efficacy data quickly. These therapies are unlikely to be curative because they were not designed for the emerging disease; however, they can provide a necessary stop-gap solution to mitigate disease severity and ease strain on the healthcare system while more specific products are developed. Gilead's remdesivir, Roche's tocilizumab (Actemra), and Fujifilm's favipiravir (Avigan) have made

headlines as therapies that can potentially reduce the severity and mortality of the COVID-19.[18,19,20] While repurposed therapies were utilized relatively well, especially in comparison to the lack of success seen in diagnostics, it might be more conducive to invest up front in these repurposed therapies, rather than acting reactively when a pandemic is identified.

**What should be done differently next time?** The use of repurposed therapies was a positive contribution to the overall pandemic response, suggesting that the speed and effectiveness of these therapies should be increased through greater upfront financial and R&D investment.[21,22,23] Clinical development of these drugs will not only benefit patients suffering from other existing viral diseases, but also will prime companies to respond quickly with repurposed antivirals while novel products must start from the pre-clinical phase.

**VACCINES** Vaccines have been a focal point of the biopharma response to COVID-19. Companies such as Moderna, AstraZeneca, Novavax, Inovio, and CureVac have all made headlines as vaccine developers who are aiming to innovate how we rapidly respond to new pathogens. Biopharmaceutical companies that have worked to produce vaccines have been an innovation engine, and the swift response by a multitude of laboratories across the world has been a bright spot during this pandemic. However, as important as it is to be able to respond reactively, proactive investment and development of vaccines could allow for a swifter response.

While proactive investment in any vaccine programming will certainly move the needle for a future pandemic, the development of pan-viral vaccines could be the most powerful mechanism of proactive development. A pan-viral vaccine could confer immunity to several viruses within a family. CEPI estimates that it takes $31-68 million to get a single epidemic infectious disease vaccine from preclinical to Phase II. However, due to failure rates, 11-21 preclinical candidates are needed for a single vaccine to reach Phase II. This raises the investment needed to ~$319-469 million.[24] Pan-viral vaccines thus have the potential to be the most cost-effective, targeting multiple strains but requiring only a single development pathway. While there is a significant investment needed to get even one vaccine candidate to market, this pales in comparison to the estimated total cost of the COVID-19 pandemic, which is thought to result in a $4.1 trillion dollar deficit in this year's global domestic product, when factors such as the immediate impact to tourism, consumption, and investment are observed.[25] If pan-viral vaccines can be developed earlier, there is a greater probability that recipients will have partial or complete immunity to new viruses of the same family. Christopher Locher, CEO of Versatope, has been working to develop a pan-flu vaccine by expressing epitopes of multiple strains of influenza on extracellular vesicles. Now, they are taking their technology into the coronavirus arena.

> "Our differentiating factor is that we are making a pan-beta coronavirus vaccine. [Most vaccines in development] are strain specific. These viruses recombine and may lead to new outbreaks. Will these single strain vaccines have the ability to address this? The answer is probably not." - Christopher Locher, CEO Versatope

**What should be done differently next time?** Pan-viral vaccine development should be an investment priority in advance of new outbreaks. Not only is preemptive vaccine development more cost-effective than a pandemic response, but pan-viral vaccines also have the potential to protect against new and recombinant strains that single-strain vaccines cannot. A pan-coronavirus vaccine pre-COVID-19 could have potentially conferred some level of immunity to recipients, resulting in a potential reduction of severity and spread (at minimum) or neutralizing immunity (at best).

## There is a misalignment of incentives that make coordinated pandemic responses difficult

The three key learnings discussed so far from COVID-19 make one fact abundantly clear: to be able to respond to future threats effectively and quickly, an expansion in ID R&D is needed. However, non-communicable diseases (NCDs) have often represented a more promising opportunity, and this translated pre-pandemic in a lack of incentives for private institutions to invest in ID R&D. Corporate R&D departments cannot be expected to dedicate resources proactively to an unseen future pandemic, especially when this requires a sizable investment and multiple hurdles, such as intellectual property rights, biosafety requirements for production facilities, and coordination and funding of clinical trials.[26] However, society only stands to benefit from proactive corporate R&D efforts in this arena, as the private biopharmaceutical sector has the expertise, facilities, and resources to innovate and commercialize viable solutions. This misalignment of corporate and societal incentives has

made the response to a novel disease outbreak less efficient as it has required for much of the ID development to be done reactively when there is a known development opportunity rather than proactively when investment risks are much higher.

Because global manufacturing capacity is finite and driven by demand, companies cannot independently shift resources away from their other products for proactive ID investment.[27] On the other hand, governments have more available financial resources and a mandate to anticipate global health threats, but may lack the specific infrastructure to develop ID-based vaccines and therapeutics *en masse*. However, by working together, governments can supply the financial incentive needed for proactive corporate ID R&D to be viable, in exchange for reaping the benefits of the biopharmaceutical industry's already existent infrastructure and drug development expertise. The solution to preparing for future pandemics thus becomes public-private partnerships.

## Public-private partnerships are key for ensuring effective pandemic response

COVID-19 has shown that biopharma companies are not always in a position where redirecting bandwidth to ID research is possible. On the other hand, the pandemic has shown that governments are willing to divert and contribute large amount of resources towards pandemic response. Herein lies the potential for a symbiotic relationship where public-private partnerships provide the necessary respective incentives and expertise to adequately respond to a pandemic. Public-private partnerships can be a key tool of pandemic response in three ways: through the funding efforts of institutions such as BARDA and CEPI, master protocol design from partnerships such as ACTIV, and through rapid regulatory pathways.

**FUNDING** Institutions such as BARDA and CEPI are critical to pandemic response because they provide the necessary funding for private R&D.[28,29] Without these institutions, private companies would have to take on 100% of the development risk for new products; this can limit the response capabilities of a private company as they must weigh the costs and benefits of responding to an ID outbreak with the potential to see a return from their efforts.[30] Previous novel disease outbreaks, such as Ebola, have resulted in large losses to pharma companies as the disease threat was contained before products could be developed; with no demand for the developed product, these R&D efforts have largely resulted in shelved products or abandoned leads. As these companies are for-profit and have a fiduciary responsibility to their shareholders and their employees, it is difficult to ask them to independently put huge investments into risky R&D at the expense of their current pipeline and manufacturing.

**MASTER PROTOCOLS.** Master protocols are necessary in a pandemic in order to rapidly test multiple promising therapies while producing statistically significant data.[31,32,33] Master protocols have multiple arms tested simultaneously, allow for arms to be added and dropped as needed, and make it possible for centers to join the trial regardless of geography.[34,35] Small, scattered, and underpowered trials can slow virus response efforts by producing data that cannot be reliably used or interpreted by regulators.[36.37] The global WHO SOLIDARITY, the US NIH ACTT, and the UK NHS RECOVERY, PRINCIPLE, REMAP-CAP, and ACCORD studies are all master protocols developed to analyze efficacy of COVID-19 therapies or vaccines and are a key part of the ongoing clinical development efforts.[38,39,40,41]

**IMPROVED REGULATORY ACCESS** None of the recommendations discussed in this paper can ultimately deliver their benefits without an effective and fast regulatory pathway. The COVID-19 pandemic has demonstrated that there is a balance between fast access and patient safety that needs to be better managed. Mechanisms of rapid approval that were instituted for COVID-19 were shown to be fallible and imperfect. The prime example of this was hydroxychloroquine, which was given an EUA by the FDA based on limited and anecdotal data; this EUA was later retracted due to lack of efficacy and concerns of harm. Despite the shortcomings of the FDA in their handling of the EUA during COVID-19, rapid access is an important program that should be learned from and built on during non-pandemic times. Earlier in June, the FDA Commissioner Stephen Hahn held a briefing where he announced that the FDA will look to permanently implement some of the policies instituted during COVID-19. These changes include support for decentralized clinical trials, greater use of telemedicine, work related to LDTs, and use of real-world evidence to adjust authorizations. Improving regulatory access via prioritizing and adjusting standard approval pathways augments the partnerships between the FDA and companies and increases response effectiveness.

**What should be done differently next time?** Funding from institutions such as CEPI and BARDA can help mitigate the

risk of wasted R&D efforts, incentivizing pharma companies to employ the best talent, technology, and resources toward solving the problem, which is ultimately in the best interest of all people. If corporations, governments, and wealthy individuals proactively donate to public-private partnerships that grant ID funding, then funds will be available to lessen the impact of and potentially prevent future outbreaks. Master protocols avoid issues of statistical insignificance, lack of coordination, and delays in response. They ensure that resources are directed to only the most promising clinical assets, increasing the likelihood that sound scientific, clinical, and regulatory decisions can be made. In the future, master protocols should be implemented earlier and coordinated with other public-private. Finally, as long as the rigor of safety and efficacy analyses can be maintained, faster approval pathways benefit all parties, including patients who are awaiting access to novel therapies.

## Conclusion

The world was unprepared for COVID-19. Our legal, health, and physical infrastructure were insufficient to respond to this disease effectively. The next pandemic will come, and to prevent us from being blindsided again, concrete steps can be taken now. Antiviral libraries can be built, pan-viral vaccines can be developed, public-private partnerships can allocate funding to institutions doing proactive work, and the FDA can amend protocols on rapid access and diagnostics approvals.

Even as pandemic response effectiveness increases in the future, it will be key to continue to analyze the COVID-19 response around the world. Equitable access to vaccines and resources is not possible so long as global manufacturing capacity remains at current finite levels. Countries lacking in resources will continue to have acute shortages as they have limited capacity to produce or purchase supplies, and countries with manufacturing capacity can be expected to reserve supplies for their own populations first. COVID-19 has provided a window into a resurgence of IDs in our changing world, and it is up to us to learn from present experiences to address those that have yet to come.

## Let's talk.

Olivia Hunter is an Associate Consultant at Bionest Partners. Email: ohunter@bionest.com

Julius Steffen is a Principal at Bionest Partners. Email: jsteffen@bionest.com

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