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Running ahead of Pandemics: Achieving In-Advance Antiviral Drugs

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Three months into the COVID-19 outbreak caused by a novel strain of coronavirus (SARS-CoV-2), the world is still in search of an effective therapeutic drug. Experimental drugs developed for other infections, such as Gilead's remdesivir, have been repurposed with unclear success.[1] A recent small study suggests that hydroxychloroquine and azithromycin used in combination may speed up recovery.[2] However, if any of these repurposed drugs prove effective, it will be a matter of good fortune, not good preparedness. We must shift from the hope of *just-in-time drugs* toward the promise of *in-advance* therapeutics by developing broad-spectrum drugs.

These drugs, however, confront a market failure: what firm will invest millions developing a drug for a nonexistent pandemic market? To overcome this confrontation, public policy can introduce adequate incentives for these investments to occur. I propose adopting innovation prizes with awards large enough to justify investments in broad-spectrum antiviral drugs developed up to phase III clinical trials in the FDA drug approval process. I also emphasize the importance of starting this effort with pathogen families of known pandemic potential, such as respiratory viruses.

JUST-IN-TIME DRUGS ARE TOO LATE

The current approach to pandemic drugs has been to create or repurpose a therapy immediately after a novel outbreak has been identified. Many aspects of the COVID-19 pandemic show progress along this path. Viral genome sequences were published within weeks,[3] and drug candidates were suggested quickly thereafter.[4] In the United States, the FDA enabled emergency-use authorization for experimental drugs. Clinical trials of remdesivir, interferons, monoclonal antibodies, ACE inhibitors, and hydroxychloroquine have all been registered, although many have not yet recruited patients.[5]

Nonetheless, pursuing just-in-time drugs is not a public health strategy; it is a desperate response to the pandemic. Developing vaccines is hard, and it takes far more time than repurposing existing drugs. Yet the latter task is not easy either: as pharmaceutical companies and regulators scramble to test and approve existing drugs in record time, a costly quarantine is society's only option to mitigate the spread of COVID-19.

Making matters worse, the world is past the early stages of the outbreak, when therapeutic drugs are most valuable for containment in the absence of vaccines. There are several drug candidates,[6] but proper testing requires time, particularly when testing is performed on humans. And during intense testing processes, companies are likely to clear their inventories and production pipelines. For example, Gilead was initially supplying remdesivir for COVID-19 patients via compassionate-use requests, but owing to the demands of running accelerated clinical trials, it has now discontinued the practice.[7]

While the world may be forced to wait until an outbreak occurs in order to create a vaccine, therapeutics such as antivirals can and should be created in advance.

THE CALL FOR IN-ADVANCE THERAPEUTICS

The traditional antiviral paradigm involves creating a drug that targets a unique aspect of the specific virus of interest, such as a protein. This targeted approach is termed *narrow spectrum* and cannot be created in advance. Consequently, the medical community needs—and currently lacks—a class of drugs designed for emerging viruses of pandemic potential. These *broad-spectrum* drugs that target entire viral families can be developed as individual drugs or platform technologies.[8]

Just before the outbreak of COVID-19, researchers at the Johns Hopkins Center for Health Security stated that "broad-spectrum [antiviral] therapeutics should be pursued given their potential value."[9] The World Health Organization's *Research Needs for the Battle against Respiratory Viruses (BRaVe)* research agenda specifically identifies "broad-spectrum antivirals against emerging viral threats (e.g. interferons for novel coronavirus)" as a priority.[10] The National Institute of Allergy and Infectious Diseases has, over the past decade, provided upwards of $250 million in funding to study potential broad-spectrum antiviral drugs. This funding has prompted basic scientific breakthroughs in viral targeting such as next-generation nucleotide and nucleoside analogs and inhibitors, host-targeting approaches, and strategies that leverage findings from RNA interference.[11]

Broad-spectrum therapies are not only feasible; they may even be more cost effective than the traditional "one bug, one drug" approach.[12] Vincent Racaniello, professor at Columbia University, notes, "We could have a broadly acting antiviral that targets [the coronavirus RNA polymerase]."[13] It is within the realm of scientific feasibility to create a catalog of antiviral drugs against every discovered viral polymerase, for example. Riboscience, a California-based company, was founded with the goal of creating a platform for developing such a roster of drugs.[14]

Broad-spectrum antiviral drugs or drug platforms that are developed in advance of outbreaks provide the opportunity to complete testing before pandemic occurrence. Preclinical testing in both cellular and animal models could thus be performed systematically, in advance. Human testing could also take place in advance. Phase I testing for safety and dose determination does not require viral infection. Phases II and III both test efficacy against infection, which could, at minimum, be partially completed using similar viral strains, such as those within the same family.

Design and testing of broad-spectrum antivirals has been achieved before. Alisporivir is a broad-spectrum antiviral that was shown to have activity against multiple pathogens, including dengue and SARS-CoV.[15] It is not currently available, as it was brought to phase III trials only for hepatitis C virus, not viruses of pandemic potential such as coronaviruses. More importantly, Novartis pulled out of acquiring alisporivir in 2015 because it deemed anti-infection drugs broadly unprofitable, confirming the market failure problem.[16] Favipiravir, also a broad-spectrum antiviral, was successfully approved in Japan as a treatment for various influenza strains and is stockpiled there for flu pandemics.[17] Clinical trials are underway to test favipiravir against COVID-19.[18] If those tests are successful, it will be the clearest indication yet that in-advance therapeutics works.

THE MARKET FAILURE FOR PANDEMIC DRUGS

Pharmaceutical firms lack market incentives to develop drugs for pandemic scenarios; these are rare events that portend unreliable revenue streams. Had a company such as Riboscience developed a drug against the coronavirus family, it would have lacked a buyer on the commercial market. Hence, it decided to prioritize other drugs.

Even if a severe pandemic does occur, driving up demand, companies could correctly foresee that intellectual property rights will be waived during the crisis. Such concerns have historical precedent: in 2005 during the H5N1 avian influenza outbreak, UN Secretary General Kofi Annan questioned whether Roche's patent on Tamiflu should be respected. Gilead's remdesivir may work for COVID-19, and Gilead's CEO has stated that the company "will not get into a patent dispute" with other companies that attempt to produce it generically.[19]

Firms would hardly be inclined (or able) to extract high prices during epidemics. This also is why investment structures suggested for similar drugs, such as options markets for antibiotics, are unlikely to work, as most investors would eschew obtaining windfall profits from the suffering inflicted by a pandemic.

Recognizing this market failure, the US government created the Biomedical Advanced Research and Development Authority (BARDA) to fund development of medical countermeasures for biological threats, including pandemics. However, much of BARDA's budget has been allocated by congressional vote after outbreaks, such as those of Ebola and Zika. Dr. Joe Larsen, previous

acting director within BARDA, stated, "Responding to an emerging infectious disease event is not something easily done, or responsibly done, with supplemental funding from Congress."[20] BARDA will succeed only with up-front funding that can be flexibly deployed far in advance of epidemics and long after them.

Of note, the Defense Advanced Research Projects Agency developed a similar program. Its Pandemic Prevention Platform program funds platform technology for medical countermeasure development but focuses on narrow-spectrum, just-in-time solutions.[21]

Vaccine development, like broad-spectrum drugs, has long confronted the same market challenges. But there is a glimmer of hope. Under the aegis of the Bill & Melinda Gates Foundation, Gavi the Vaccine Alliance, and development economists, vaccine development has seen a resurgence. In 2007, an advance-market commitment of $1.5 billion spurred the development of pneumococcal vaccines for low-income countries, saving approximately 700,000 lives.[22] Advance-market commitments are contractually binding prizes (offered to companies) that guarantee viable markets for drugs that otherwise lack those markets.[23]

In 2017, the Coalition on Epidemic Preparedness Innovations (CEPI) launched as a global partnership between nations, private companies, and philanthropic organizations to accelerate the development of vaccines and ensure equitable access to them. It plans to achieve this through R&D prizes, advanced-market commitments, and grants, and it has announced funding for three promising vaccine candidates for COVID-19.[24]

FIXING THE PROBLEM NOW AND FOR THE FUTURE

The economic havoc of the current pandemic has created a sense of urgency for directing public investments toward novel approaches that bear promise. As vaccine advance-market commitments become well established, innovation prizes for broad-spectrum drugs too should become established, and policymakers should give such prizes serious consideration.

Prizes are being piloted by the Bill & Melinda Gates Foundation, Wellcome, Mastercard (which recently announced a $125 million COVID-19 therapeutics accelerator),[25] and smaller funds such as Emergent Ventures.[26] New prize structures have been suggested, such as the Epidemic Market Solution, which incentivizes companies by using lucrative stock options.[27]

But to achieve true in-advance therapeutics, these prizes must be awarded according to strict criteria. Rewards must first be directed toward companies that bring broad-spectrum antiviral therapeutics up to, at minimum, phase III clinical testing for a prioritized list of viral families that have pandemic potential and for which there are no vaccines, such as coronaviruses presently. A prizewinning drug must have clear-cut characteristics. It should be safe. It should substantially

reduce viral titer and transmissibility in humans when administered before infection (for prophylaxis) and after infection (for treatment). And most crucial of all, it should do so for all strains of a certain viral family or even multiple viral families. Counterintuitively, it may not need to show symptomatic improvement because many viruses (including many coronaviruses) do not cause symptoms, unlike their pandemic-strain cousins.

Per viral family, these rewards will need to be on the order of $1 billion. While this amount is a mere fraction of the economic value lost owing to a global pandemic, it does cover the opportunity cost of bringing drug candidates to market. Pharmaceutical companies and investors, particularly in the United States, normally seek to develop the next "blockbuster" drug capable of generating revenue of at least $1 billion. By pursuing in-advance therapeutics, companies and investors risk millions of dollars by hiring, completing research, and developing that could be spent pursuing those blockbuster drugs with more reliable revenue streams. Prizes compensate companies and investors for this risk.

In order to guarantee the production and distribution of drugs in times of national crisis, the government should retain the rights to the intellectual property that results from pursuing in-advance therapeutics. This patent-buyout approach builds on existing legislation. The US government has long bought desirable patents from inventors at a fair price.[28] These drugs may one day also serve as an important government defense against novel, weaponized viruses.

Planning for the long run, these innovation prizes must be kept in place even in years when no outbreaks occur, in order to continue building these capabilities. When effective broad-spectrum antivirals are developed, rewards should be transitioned to manufacturers who keep up their production capacities.

In-advance therapeutics will also require a unique pathway with the FDA. These drugs will be up for approval as treatments for diseases that don't yet exist; that is, for future pandemics. Pandemic approval by the FDA must allow for the appropriate broad-spectrum antiviral to be prescribed as quickly as possible after a novel strain is identified.

In sum, the health and economic value of pandemic drugs developed in advance of outbreaks cannot be overstated. The current lack of these drugs is largely the result of market failures, not insurmountable scientific hurdles. But as I have argued in this brief, public policy can introduce market incentives via innovation prizes to develop these drugs. These incentives should be implemented to respond to the current pandemic and as a crucial element of the health system's preparations for future crises.

ABOUT THE AUTHOR

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NOTES

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