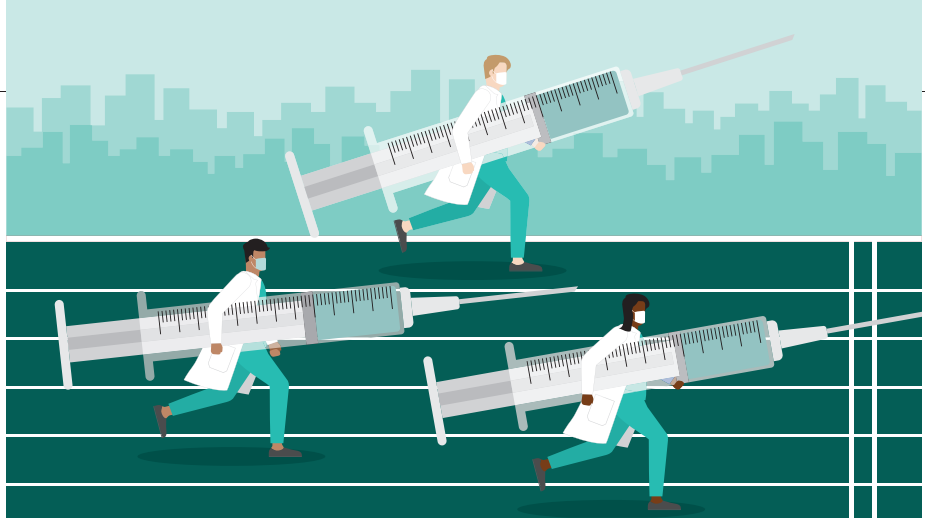

ILLUSTRATION: ADAPTED BY C. SMITH/*SCIENCE* FROM KORA_SUN/SHUTTERSTOCK

VIEWPOINT: COVID-19

Advancing new tools for infectious diseases

Therapeutics and vaccine development for infectious diseases could be transformed

By **Rajesh Gupta**

Several infectious diseases cause considerable mortality worldwide each year: Tuberculosis causes ~1.2 million deaths, diarrheal disease causes ~1.5 million deaths, and lower respiratory infections cause ~700,000 deaths in children under 5 years old (*1*). Yet the scale and speed of innovation in developing tools for coronavirus disease 2019 (COVID-19) dwarf the development of those for global infectious diseases, which disproportionally affect resource-limited countries. By August 2020, ~175 therapeutics and vaccines were in clinical trials for COVID-19 (*2*). By contrast, for 41 global infectious diseases or disease groups, only ~250 therapeutics and vaccines were in clinical trials in August 2019 (*3*). A robust product pipeline and abridged development time frame for COVID-19 has primarily been enabled by three factors: scientific advances, operational efficiencies, and large-scale at-risk financing. A clear, well-financed path from research through product procurement now exists for COVID-19, shortening timelines while increasing output. This could underpin an approach for global infectious diseases.

Recent scientific advances have revolutionized platform technologies and expanded the ability to rapidly identify therapeutic and vaccine candidates. High-throughput computational screening of molecular libraries against key pathogens and/or host targets has accelerated the ability to repurpose agents and identify entities against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, which causes COVID-19) (*4*). Candidate compounds with existing clinical safety data quickly entered clinical trials, leading to the repurposing of dexamethasone and remdesivir to treat hospitalized COVID-19 patients. Monoclonal antibodies (mAbs) can potentially provide near-immediate therapy and/or prophylaxis by bypassing the need for a host-generated immune response (*5*), and at lower costs and higher volumes than previously assumed. Vaccines have benefited from innovations in vector modalities, manufacturing, antigen design, computational biology, protein engineering, and gene synthesis (*6*). Such innovations may provide the technological basis for targeting other global infectious diseases.

In response to COVID-19, the public health and regulatory communities are streamlining clinical development. Independently funded, designed, and conducted platform clinical trials, such as Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), are structured under a single, adaptive "master" protocol to allow for continuous and consistent evaluation of multiple drug candidates, adding products as they become available and removing candidates as they are deemed futile. They also provide access to large, geographically diverse populations, and some have created or expanded operational structures in resource-limited countries (*7*). Timelines have been shortened because of accelerated regulatory reviews, flexible requirements to enter first-in-human trials, newer approaches to modeling population-specific issues, early approval mechanisms, and enhanced regulatory harmonization among countries (*8*). This increased efficiency in clinical trial execution and regulatory processes could be applied to other global infectious diseases.

Historically, investment in product development for global infectious diseases has been restricted owing to the lack of financial returns compared to more profitable areas of drug development, such as oncology. However, the threat that pandemic human coronaviruses (HCoVs) pose to the global economy, political stability, and people's lives has stimulated the private sector, public sector, and philanthropic groups to devote considerable financial and human resources to product development. Previous HCoV outbreaks led to initial development activities that were accelerated with COVID-19. Supplementing these efforts, the U.S. government has provided over $10 billion for COVID-19 therapeutics and vaccines. Other governments, including the European Union, United Kingdom, Germany, and Canada, are making substantial financial commitments, as are large funding institutions (*2*).

A fundamental principle behind this unprecedented funding is that financing for the entire product development process is made by the time a candidate enters early-stage clinical trials (*9*). This approach has mitigated the range of risks faced by different categories of developers (e.g., academia, nonprofit organizations, public-private partnerships, small biotechnology companies, and large multinational pharmaceutical companies) who may individually have widely varying risk-reward calculations. As a result, developers can simultaneously prepare for late-stage clinical trials, implement scaling up of manufacturing processes, and obtain advanced purchase commitments of large-scale supply—all during first-in-human clinical trials (*9*). Together, providing the full range of financing as early as possible in the product development process, articulating the need for multiple products, and acknowledging implicit failure of some candidates and platforms have overcome product development barriers. The result has been an extraordinary scale of therapeutic and vaccine development in the shortest time possible.

A similar product development framework could be created for global infectious diseases. Such a framework could attempt to resolve three long-standing challenges for these diseases: the lack of interest in

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developing products, resulting in a diminished initial pipeline of candidates; the large pipeline attrition points between preclinical activities and early-stage clinical trials and between early- and late-stage clinical trials (*10*) that occur because of the considerable increases in development costs of these two transition points; and the extended timelines for product development. If these challenges are addressed, a more robust initial pipeline could be created, more candidates could advance to early- and late-stage clinical trials, and more products could be approved in a shorter period.

A robust pipeline for global infectious diseases should include repurposed agents, mAbs, new chemical entities, and vaccines. Each of these categories possess strengths and limitations; thus, each may not prove beneficial for every disease. Repurposed agents may have existing preclinical data and clinical safety experience, putting them on the fastest development timelines. mAbs targeting proteins encoded by highly conserved regions of a pathogen's genome—thereby minimizing escape mutations and maximizing strain coverage—can be isolated from patients and modified to enhance their activities, for example, to extend half-life and induce host immune responses. New chemical entities could target families of pathogens to create "one-drug-multiple-bug" approaches to replace "one-drug-one-bug" approaches. Traditional vaccine platforms have a history of clinical validation and scaled production capacity. Emerging nucleic acid–based vaccine systems have promise for generating a candidate upon availability of a genomic sequence.

Several factors must be considered to rapidly build and advance such a pipeline. Arguably the most critical factor is to incentivize all development groups and encourage aggressive competition. Public sector and philanthropic financing should address the cost of research, clinical trials, manufacturing, and supply agreements, and such financing should be available at the earliest possible part of the product development process. This is essential to overcome developers' decision to avoid product development because of lack of a clear revenue model. This financing, in turn, could stimulate the levels of investment and activity from the private sector observed in COVID-19, including public-private partnerships to advance candidates. A fundamental biological understanding of coronaviruses existed prior to COVID-19 and is necessary to drive product development, but a similar biological understanding needs to be improved for many global infectious diseases (*11*). While under development for COVID-19, predictive, validated preclinical assays, animal models, and human challenge models for infectious diseases would provide faster, cost-efficient methods to eliminate candidates earlier in the development cycle (*12*, *13*).

Moreover, implementing high-quality, decentralized clinical trials and using existing clinical trial networks could reduce the need for each developer to create complex multicountry clinical trial processes and infrastructure while still maintaining consistent evaluation methods (*14*). Machine learning could help optimize clinical trial design and identify populations most likely to benefit from a candidate, thereby reducing the large sample sizes currently required for late-stage clinical trials (*15*). Consideration should be given to what accelerated and flexible regulatory processes may be adopted from COVID-19, and which regulatory agencies should serve as benchmark approvals for those diseases that predominantly affect resource-limited settings. The manufacturing supply chain may need to be improved for some technologies facing global constraints. Additionally, access, affordability, and availability will need to be addressed to ensure that innovations reach the populations in greatest need.

Implementing this strategy is not without risk, and there are challenges to overcome. Development of predictive models and biomarkers has proved difficult with COVID-19. The risk-benefit assessment for accelerated first-in-human testing during an unfolding pandemic may differ compared to that for endemic pathogens. Global capacity for late-stage clinical trials may initially be reached quickly in resource-limited settings. As seen with hydroxychloroquine, early approvals based on limited evidence can occur with compounds that ultimately demonstrate no benefit. The advanced financing available for COVID-19 candidates partially emerged from country-specific interests and, if repeated, may continue to foster inequitable access to new tools globally. Ultimately, the SARS-CoV-2 product development model may need optimization to realistically achieve success across multiple global infectious diseases.

Of the ~250 therapeutics and vaccines in clinical development for global infectious diseases, ~30% are for HIV and AIDS (*3*). The innovation in antiretroviral medicines was initially sparked by strong political will coupled with streamlined regulatory processes. Growing demand produced attractive returns from resource-wealthy countries. By contrast, the distinct regulatory pathways and government funding to address the growing problem of resistance to antimicrobial agents (such as antibiotics) could not overcome the lack of a revenue model, thereby bankrupting companies that successfully developed safe and efficacious therapies and curtailing development activities. For the recent outbreak of Zika virus beginning in 2015 in the Americas, the time frame from identification of genomic sequences to advancing a nucleic acid vaccine into phase 1 clinical trials occurred within 4 months; but the threat to high-income countries quickly subsided, resulting in stalled product development programs. After nearly 40 years of continuous outbreaks in Africa, the potential global spread of Ebola became evident during the 2014–2016 outbreak and spurred public-private partnerships that recently achieved approval of two vaccines and one therapeutic mAb combination (with a second, single therapeutic mAb under regulatory review).

Resource-limited countries are experiencing combined morbidity and mortality impacts from COVID-19: from the disease itself and from other global infectious diseases, owing, in large part, to diversion of resources. Which candidates in clinical trials for COVID-19 will reach regulatory approval, what limitations may come with licensed candidates, and the success of emerging technology platforms are all unknown. However, COVID-19 forced the world to construct a new product development approach, taking what was previously perceived as impossible and turning it into reality. How to implement this approach to address other global infectious diseases that continue to curtail global economic growth and devastate humanity must now be decided. ■

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