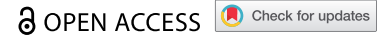


COMMENTARY



Building a global immune system

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ABSTRACT

The COVID-19 pandemic exposed global vulnerabilities to emerging infectious diseases, heralded by earlier outbreaks, that did not result in appropriate investments in surveillance, international collaboration, and response. We propose specific steps that should be taken to reduce future risks to public health, economic and political stability, and food security.

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Discussion

In 2002, Sir Martin Rees, the current President of the Royal Society, then Fellow of Trinity College, Emeritus Professor of Cosmology and Astrophysics at the University of Cambridge, and Astronomer Royal, made a bet “That by the year 2020 an instance of bioerror or bioterror will have killed a million people.”¹ Although the COVID-19 pandemic proved that bet, we have not yet made the investments needed to prevent future threats. SARS-CoV-2 is not the first and will not be the last challenge to our survival as a species. Over the past 40 years we have seen the emergence of HIV/AIDS, West Nile virus, Nipah, Zika, SARS, MERS, and antibiotic resistant bacteria. The risk will further increase as escalating travel and trade facilitate rapid global dissemination of infectious agents, disturbances in wildlife habitats result in exposure of humans and domestic animals to novel viruses, and changes in climate expand the geographic range and prolongs the duration of activity of phlebotomus insects such as ticks and mosquitoes that harbor infectious agents.² We have already lost over 5 million lives³ to the COVID-19 pandemic worldwide since January 2020.⁴ Up to 33% of the 250 million infected will have long-term disability, with 40% of those people never having a record of any long-term symptoms prior to COVID-19 illness.⁵ The economic cost is projected to reach \$22 trillion.⁶

In recognition of the observation that the majority of emerging infectious threats to human health originate in wildlife, national research agencies and foundations have made large investments in programs that investigate the spectrum of viral flora in bats and nonhuman primates in regions predicted to be hot spots for emerging infections. Examples include the United States Agency for International Development PREDICT program and the proposed extension of PREDICT, the Global Virome Project that would catalog the diversity of viral flora worldwide.⁷ The objectives of these programs are to build a repository and a database that can enable discovery of links

between infections in wildlife and humans as well as methods for proactive detection of potential risks. Viruses similar to SARS-CoV-2 have been reported under the auspices of PREDICT; however, it is unclear that these findings had an impact on the trajectory of the COVID-19 pandemic or will mitigate the risk of future pandemics. What was enormously helpful in the early days of the COVID-19 pandemic was the release of sequence data by Edward Holmes of the University of Sydney, on behalf of a group led by Yong-Zhen Zhang of Fudan University in Shanghai, from a human victim on the pre-publication website Virological.org.⁸ Within hours scientists worldwide were designing diagnostic tests and vaccines.

A fundamental challenge in the rationale for cataloging viruses is that we do not have the wisdom to predict based on sequence alone which viruses will become efficient at cross species transmission. These programs also do not provide insights into bacteria, viruses, and fungi circulating in humans or domestic animals; antimicrobial resistance; microbial threats to food security; or misuse of synthetic biology. An alternative and less speculative approach is to build on the International Health Regulations of 2005 signed by all member states of the United Nations by investing the resources needed to enable rigorous national and international surveillance and response through capacity building and collaboration.⁹ Over the past 20 years, the authors have worked in several countries in Asia, South America, and Africa where our counterparts are eager to prospectively survey hospitals, clinics, and abattoirs, and to investigate outbreaks in humans and wildlife. Many of these investigators have already banked specimens during outbreaks for analysis. The functional impediments to moving forward with these programs are a lack of trained personnel (particularly in bioinformatics), biocontainment facilities, sequencers, and supplies. There are sociopolitical impediments as well. What these investigators tell us is that the colonial model wherein investigators from wealthy nation states visit,

extract samples and intellectual property, and produce vaccines and drugs that are not accessible in the developing world is not tenable. Local investigators are happy to share data but want to drive the work themselves and receive appropriate recognition for their contributions.

A framework for global surveillance alone is insufficient to ensure a robust global immune system. The follow-through response is also critical. The development of diagnostics, drugs, and vaccines requires access to human subjects, samples, and clinical metadata, that in turn, require human subjects approvals, material transfer agreements, and the collection and curation of samples from well characterized subjects in biorepositories. Although sample collection is labor intensive and expensive, there is little glory in the effort. We must find better ways to recognize and support the clinicians and archivists who are essential partners in basic and clinical research. Interventions like drugs, monoclonal antibodies, convalescent plasma, or vaccines, require data safety monitoring boards, institutional and national regulatory approvals. It can take months to secure these approvals at a single site. This is challenging in peace time, but more arduous during a pandemic when institutions are short-staffed and personnel must work remotely. As the pandemic epicenter shifts, it may not be possible to find subjects for an appropriately powered clinical trial without moving beyond the approved catchment area. Finally, as new interventions come on line, subject numbers must increase accordingly to reflect the potential for these interventions to impact results.

The COVID-19 pandemic has revealed vulnerabilities that have been apparent for decades to those working in the fields of biosecurity and emerging infectious diseases. They were highlighted for the global community by the IHR of 2005, and in the United States by the reports of the National Biodefense Advisory Subcommittees convened by Presidents George W. Bush and Barack Obama.¹⁰ Academic institutions, cities, states, countries, and foundations are launching pandemic prevention initiatives. How these initiatives will complement one another is unclear. As it is unlikely that all of them will survive, it is important to ensure that those that do will cover the bases. We feel strongly that the World Health Organization is the appropriate organization to coordinate these initiatives, and ensure that they are adequately resourced, appropriately designed, and complementary rather than duplicative. Some readers may feel that the WHO could have better managed its response, particularly early in the pandemic. This criticism should be viewed in light of the agency's need to balance the relative merits of carrots and sticks in promoting its mission.

Diagnostics and surveillance

As per the IHR of 2005, each nation state must have the resources to detect infectious threats within its borders and an obligation to transparently share the information with the global public health community. Meeting these objectives will require investments in training, equipment, supplies, and methods for continuous sampling of humans and animals with infectious diseases. Sites should be selected and sampling strategies developed by epidemiologists and statisticians to maximize the probability of capturing early cross-species

transmission events and evolutionary adaptations that increase rates of transmission, increase morbidity or mortality, or result in diminished efficacy of diagnostics, drugs or vaccines.

Data sharing

Access to resources for diagnostics and surveillance should be predicated on agreement to share data on what infectious agents are circulating and where, full genomic sequence of those agents, and information on transmissibility, incubation periods, spectrum of illness, insights into management. To ensure early detection of threats to public health, cloud-based bioinformatics platforms should be used for sequence analysis. Individuals who collect sequence data must be acknowledged for their contributions and indemnified in the event of inadvertent inaccuracies. Governments, organizations, and companies that access this data repository for the development of countermeasures must be required to equitably share intellectual property and access to countermeasures.

Globalization of regulatory approvals

An international health regulatory agency should be created with the mandate of facilitating trials and the approvals of diagnostics, drugs, and vaccines, and for establishing criteria for quality control and performance. This agency would not only expedite the development of countermeasures but also enable the early identification of false cures that waste resources and undermine confidence in public-health authorities. We envision proactive development of internationally approved consent and assent forms, fillable digital protocol forms, human subjects and data safety monitoring boards. All documents should be translated into multiple languages (and back translated to ensure accuracy). We appreciate that there will be pushback from some national regulatory agencies; however, there is precedent for regional and international tribunals in law that might serve as model for building a correlate agency for promoting public health. A recent publication in *Lancet* from a Global Health Diplomacy and Cooperation task force highlighted the importance of building a global agency with this mandate.¹¹

Vaccine platforms

As of December 2, 2021, only 7 of 135 vaccines listed in clinical trials by the World Health Organization (WHO) are intranasal.¹² All of vaccines approved for use by the WHO, including those that have received emergency use authorization by the United States Food and Drug Administration, require intramuscular injection. Although large, rigorous clinical trials confirm that these vaccines reduce the risk of severe disease, they have been less successful in preventing virus transmission. The majority of antibodies elicited by intramuscular vaccines are of the IgM- (early) or IgG-type (late) that circulate in blood and tissues. A small minority are the IgA type that are distributed at the mucosal surfaces of the nose, eyes, and mouth where we are most vulnerable to respiratory viruses like SARS-CoV-2. In contrast, intranasal vaccines are most

efficient at inducing the production of IgA antibodies that have the capacity to bind viruses before they invade mucosal surfaces. In addition to reducing the risk of the initial infection, IgA antibodies may also reduce ongoing transmission to other people by binding to progeny viruses in the nose and mouth and upper airways in the event that they do not fully block infection in the vaccinees. Additional challenges with intramuscular vaccines include hesitancy, production, and delivery. A study in the United Kingdom of more than 15,000 adults reported an injection phobia in approximately 10% of vaccine hesitant individuals.¹³ A shift to less invasive intranasal vaccines should result in improved compliance. Furthermore, intranasal vaccines will be easier to deploy because they should not need highly trained vaccinators or the level of sterility required with injectable vaccines. One of us argued the importance of this vaccine strategy in a recent editorial.¹⁴

Conclusions

As we finished the draft of this article, the WHO announced the advent of the Omicron variant, the latest variant of concern. Stock markets tumbled and both the European Union and the United States restricted travel from South Africa. We expect that any new vaccines needed for this and future variants will be developed even more rapidly than for the original strains. Nonetheless, ensuring global biosecurity is a marathon as well as a sprint. While the world focuses on COVID-19, new influenza viruses, arboviruses, tick borne agents, antibiotic resistant bacteria, and veterinary pathogens are continuously emerging. We need the scientific, political and economic infrastructure required for a global immune system that anticipates, detects and responds to all threats to human health, and food security. An obvious question is how these critical initiatives will be funded. We initiated a program for capacity building, surveillance, discovery and data sharing with support from the Skoll Foundation, anonymous donors, and intramural in kind support from the US National Institutes of Health. The Global Alliance for Preventing Pandemics (GAPP) is already yielding insights into the distribution of SARS-CoV-2 variants, and the utility of diagnostic tests and interventions.¹⁵ We are aware of similar efforts from other teams and appreciate that consolidation would enhance efficiency. A financial model for ensuring the long-term viability or expansion of such programs is beyond the scope of this article but should consider the global cost of over 5.5 million lives³ and \$24 trillion in economic product¹⁶ as we enter year three of the pandemic. If we collectively allocated through national and philanthropic contributions even 0.1% of the losses we have to date, sum of \$25–50 billion^{17,18} should be sufficient to build the global immune system we need.

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