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The USA's response to the 2014 Ebola outbreak could have informed its COVID-19 response

Despite multiple warnings and the inevitability of infectious disease outbreaks, preparedness has been undervalued, underfunded, and largely treated as optional in the USA. From severe acute respiratory syndrome in 2003 to Ebola in 2014, the USA has confronted many outbreaks—each should have served as a wake-up call to the importance of preparedness, knowing that these were not one-off events but part of a looming trend. Since their creation 15 years ago, the International Health Regulations of 2005 have been used five times to declare a Public Health Emergency of International Concern.

Preparedness is, by definition, proactive. Yet the way we often respond to outbreaks is reactive. To reap its remarkable dividends, preparedness must remain an active and ongoing commitment. Investments in preparedness will strengthen health-care systems and better protect health-care workers all across the globe. Emerging infectious diseases do not respect borders, making it critical that such preparedness happens in unison, with coordination among national and international partners.

Yet, as we have learned with COVID-19, preparedness alone is not enough. During outbreaks, public health experts must be given the platform to provide politicians and the public alike access to prompt and accurate information. As a global community, we must recognise that our response to such outbreaks must be global—no country or community is safe until we are all safe. Outbreaks are inevitable, and it is essential that we recognise these fundamental truths about the role and importance of preparedness before we confront the next pandemic.

There are also clear financial benefits to prioritising preparedness. Since October, 2020, the COVID-19 pandemic has an interim economic price tag of US\$16 trillion in the USA.¹ Had the USA invested just an additional \$5 per person annually in preparedness,² both domestically (\$1.65 billion) and internationally (\$39 billion), it would have taken 970 years to spend as much on investing in global preparedness as the USA is hemorrhaging in response due to COVID-19.

There are foundational elements in epidemic preparedness that should have been gleaned from the USA's previous outbreak responses and subsequently applied to all future health threats, including COVID-19. Five lessons learned from the USA's response to the 2014 Ebola outbreak should have informed the country's COVID-19 response, given its roles in responding to both epidemics previously and currently.

First, infectious disease outbreaks expose the shortcomings in health-care systems. The Ebola outbreak pointed to gaps in training and resources as not all US hospitals were ready and equipped to manage a patient with suspected or confirmed Ebola. With COVID-19, all 6090 US hospitals became battlegrounds. Given that pandemic preparedness has not been part of routine health-care delivery, nor has there been an incentive to build a better infrastructure, there must be specific federal funding allocated that is sustained in perpetuity to ensure biopreparedness. A return to pre-pandemic normal is what got us here in the first place. Americans must invest in long-term solutions, build back better, invest in preparedness, and sustain the gains. Regardless of the cost, this investment will pay massive dividends during the next pandemic.

Second, health-care worker safety must be prioritised. Protecting the health-care workforce should always be a top priority. Simply put, there is no patient care without providers. Health-care facilities that were caring

for patients with Ebola had a provider-centred approach, containing the virus within a dedicated unit and with a limited number of health-care personnel as part of the care team. With COVID-19, nearly every provider is on the front line and must be supported, and the strategy must be shifted from containment to community risk mitigation. Health-care worker safety goes beyond just physical safety. It must also encompass psychological and mental health support.

Third, a coherent national plan is vital to combat a pandemic, and collaboration with national and international partners, including the US Centers for Disease Control and Prevention, the US Agency for International Development, and WHO—all of whom collaborated at the forefront of the fight against Ebola in 2014—is necessary. That collaboration was two-fold: to work together in mitigation and containment of the contagion, and to share knowledge, best practices, and lessons learned that would better inform processes, public health guidance, and health-care responses. Responding to pandemics by prioritising nationalistic tendencies over global goodwill is doubly damaging—it undermines the USA's important leadership role in global health, but also makes the USA less safe for Americans.

Fourth, health experts must be placed at the forefront to educate the public. Science and risk communication during a public health crisis is crucial. With every epidemic comes the contagion of misinformation. Health experts, such as those in public health and health-care services have a central role in addressing misconceptions, risk behaviours, preventive measures, and providing the latest science-based information. Although the risk of Ebola transmission within the community in the USA was low in 2014–16, the public perceived the threat as much greater,³ requiring a coherent, one-voice approach from the federal government to better inform the public. COVID-19 is, however, a substantial public health



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threat with ongoing community transmission in the USA. Sharing conflicting information and largely politicising the pandemic has led to greater loss of trust in science and life-saving public health measures with constant undermining of public health professionals.

Finally, training and hands-on experience are critical. During the 2014–16 Ebola outbreak in west Africa, academic (medical and public health) institutions across the world contributed faculty and staff to aid the response. This global assistance was crucial to ending the outbreak and provided unparalleled real-world and hands-on experience to thousands of health professionals who would subsequently use those skills to lead future responses at home and abroad. Although case studies and simulated exercises are helpful didactic tools in preparedness and response, they do not reliably mimic the on-the-ground complexity of response activities during a disease outbreak. Compared with their counterparts across the globe, the academic institutions and public health schools in the USA were more restrictive and less likely to send faculty and staff, often for logistic or legal reasons. This situation meant that the USA had fewer front-line providers with real-life experience in a rapidly changing disease outbreak. Had more Ebola-experienced providers been on the front lines during the early stages of the COVID-19 pandemic, we would have responded better, faster, and more efficiently.

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- 2 Global Preparedness Monitoring Board. A world in disorder. Global Preparedness Monitoring Board annual report 2020. Geneva: World Health Organization, 2020.
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Sex-disaggregated data in COVID-19 vaccine trials

As the first wave of COVID-19 vaccines enter the market, and global immunisation programmes are implemented, the time is right to remind researchers and regulatory agencies of the critical importance of including biological sex as a variable in trial data analysis and reporting.¹ The phase 3 Oxford–AstraZeneca trial interim report indicates more participation from women, which the investigators attribute to a recruitment focus on health-care workers,² but they have not yet reported or discussed how biological sex could influence the data. Future reporting of sex-disaggregated data and a discussion of how sex factors influence the trial outcomes would benefit regulatory and public decision making and the design of mass vaccination programmes.

Why is biological sex relevant, and sex-disaggregated analysis important? A growing body of research highlights the influence of biological sex in clinically relevant health outcomes, including sex-specific differences in immunity, pharmacology, and vaccines outcomes (side-effects and efficacy).³ In vaccine studies, cisgender females tend to develop higher antibody response and, relatedly, higher efficacy and more side-effects, suggesting the need for sex-differentiated dosing regimens.^{3,4} Previous influenza vaccine research suggests that women can produce the same immunological response to half-dose vaccine as men do to full dose.⁵ According to research findings in preprint,⁶ sex-based differences in innate and adaptive immunity in SARS-CoV-2 infections are probable contributors to the increased risk of intensive care unit admission and overall mortality in men, and increased reports of long-COVID symptoms in women. These hypotheses and

evidence on the sex determinants of immune responses could also be present in COVID-19 vaccine-induced immunity and adverse outcomes.

Taking a cue from the remarkable achievements in vaccine innovation and research during the COVID-19 pandemic, we have an opportunity to course-correct the integration of biological sex as a core variable in study design, analysis, and reporting. Sex factors, including sex-disaggregated analysis and reporting, are still neglected across the continuum of medicines research and regulation.⁷ This is also the case in COVID-19 trial data reporting. According to an evaluation in preprint⁸ of nearly 2500 COVID-19-related studies, less than 5% of investigators had pre-planned for sex-disaggregated data analysis in their studies. We note and applaud those vaccine trial reports that did include sex-disaggregated primary outcomes data.^{9,10} A further mention of sex-disaggregated adverse events and secondary outcomes in future reports would be beneficial. This would collectively set an analysis and reporting benchmark not just for the many COVID-19 candidate vaccines in the research pipeline, but also for all future pharmaceuticals, biologics, and other medical interventions.

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