Preparing for the Next Pandemic — Expanding and Coordinating Global Regulatory Capacity

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Diagnostics, therapeutics, and vaccines are fundamental interventions necessary for responding to public health emergencies. They are also chemically and functionally complex, and evidence of their efficacy and safety must be evaluated by independent experts. In the United States, this role is filled by the Food and Drug Administration (FDA) and its constituent centers and specialized scientists.

This kind of scientific expertise is costly, and worldwide there are relatively few regulatory bodies like the FDA to review evidence supporting licensure of medical products. For vaccines, for example, the World Health Organization (WHO) considers only nine national regulatory bodies to have the full set of functions and powers to qualify as "highly performing." The European Medicines Regulatory Network, which includes the European Medicines Agency (EMA), represents a tenth, regional highly performing authority for vaccines. All these agencies are in high-income countries. The regulatory systems of 73% of WHO's member states have not yet achieved maturity level 3, meaning that they cannot guarantee their country's population that medical products are quality-assured. Because regulatory capacity is limited, when public health emergencies arise, only a few regulatory agencies are empowered to approve diagnostics, therapeutics, and vaccines for procurement and distribution by international organizations.

We advocate that three measures that could be taken by the WHO and global health leaders to support and expand regulatory capacity during public health emergencies would help achieve equitable access to essential medicines necessary for response. We focus here on vaccines, but similar limitations and constraints apply to diagnostics and therapeutics.

The concentration of regulatory capacity in wealthy countries causes supply bottlenecks and hoarding. During the Covid-19 pandemic, the United States and the European Union possessed the manufacturing capacity to produce vaccine doses domestically, the financial resources to pay vaccine producers in advance, and well-developed national regulatory authorities to review evidence for emergency use. China and India produced vaccines, but China's went mostly to upper-middle-income countries during the pandemic's acute phase because they had not been licensed elsewhere, and India's were approved only late in the pandemic. Low- and middle-income countries generally lacked the capacity to produce vaccines and depended on financing from multilateral development banks and other third parties, which limited their procurement support to vaccines certified by the WHO's Prequalification of Medicines (PQ) program.

The PQ program relies on the same set of regulatory bodies — categorized as stringent regulatory authorities — or on an emergency use listing (EUL) from the WHO, which also largely relies on stringent regulatory authorities. The EUL process technically uses criteria that are different from those that the FDA or the EMA uses for approval, but it has historically functioned poorly during emergencies and is overreliant on those agencies. Regulatory approval for five of the six Covid-19 vaccines that had been granted EULs before June 2021 was based solely on EMA review, according to the WHO. As a result, low- and middle-income countries were unable to secure funding for prepayments to vaccine producers and so could not enter into purchase agreements until later, if at all.[1] An additional 28 Covid-19 vaccines with data dossiers submitted as long as 2.5 years ago are still under evaluation for EULs.[2] This group includes vaccines with high efficacy (>90%) and safety shown in phase 3 clinical trials, such as the Abdala vaccine (Cuba). Delayed delivery of vaccine doses to low- and middle-income countries was attributed to delayed regulatory approval and to these countries signing purchase agreements later than high-income countries as a result of reliance on PQ.[3]

Despite producing large quantities of vaccines, China and India, each of whose regulatory system is designated as maturity level 3 (see table), were similarly limited by global regulatory capacity constraints. The Serum Institute of India produced large quantities of the Oxford–Astra-

Zeneca vaccine, but global access to that vaccine was conditioned on approval by stringent regulatory authorities. Furthermore, India is a major producer but can restrict exports, as it did during the Covid pandemic when the delta variant of SARS-CoV-2 severely affected its population. Insufficient data are available on which of the vaccines developed in China reached precisely which markets, but analyses of the data that do exist suggest that Chinese vaccines largely went to upper-middle-income countries such as Bahrain, Chile, and the United Arab Emirates, which had or could borrow the necessary funds.[4] Moreover, since China's regulatory authority had not yet been designated as maturity level 3, researchers raised concerns that the lack of transparency surrounding approvals in China and destination markets fueled vaccine hesitancy.

The WHO has taken steps to reduce reliance on the EMA and the FDA by creating a new framework of WHO-listed authorities to replace the designation of stringent regulatory authorities. The process for evaluating and designating WHO-listed authorities involves planning by WHO experts in Geneva, at the WHO's six regional offices, and in collaboration with in-country bureaus to ensure that the regulatory capacity of national agencies is well verified. However, continuing provisions, such as one permitting the United Nations Children's Fund and the Pan American Health Organization to procure vaccines that have been granted market authorization by stringent regulatory authorities, suggest that the norms of the old system persist.

In order to better prepare for the next global public health emergency, we argue that the WHO-managed system for prequalification and EUL must do more than create standards for assessing na-

Pandemic Regulatory Capacity.*

Country	Regulatory Authority	Maturity Level	Scope of Products
China	National Medical Products Administration (NMPA)	3	Vaccines (producing)
Egypt	Egyptian Drug Authority (EDA)	3	Vaccines (producing)
Ghana	Food and Drugs Authority (FDA)	3	Medicines; vaccines (nonproducing)
India	Central Drugs Standard Control Organization (CDSCO)	3	Vaccines (producing)
Indonesia	National Agency of Drug and Food Control (BADAN POM)	3	Vaccines (producing)
Nigeria	National Agency for Food and Drug Administration and Control (NAFDAC)	3	Medicines; vaccines (nonproducing)
Saudi Arabia	Saudi Food and Drug Authority (SFDA)	4	Medicines; vaccines (producing)
Serbia	Medicines and Medical Devices Agency of Serbia (ALIMS)	3	Vaccines (producing)
Singapore	Health Sciences Authority (HSA)	4	Medicines; vaccines (nonproducing)
South Africa	South African Health Products Regulatory Authority (SAHPRA)	3	Vaccines (producing)
South Korea	Ministry of Food and Drug Safety (MFDS)	4	Medicines; vaccines (producing)
Tanzania	Tanzania Medicines and Medical Devices Authority (TMDA)	3	Medicines; vaccines (nonproducing)
Thailand	Food and Drug Administration (FDA)	3	Vaccines (producing)
Turkey	Turkish Medicines and Medical Devices Agency (TITCK)	3	Medicines; vaccines (producing)
Vietnam	Vaccine regulatory system involving the Drug Administration of Vietnam (DAV); the Administration of Science, Technology, and Training (ASTT); the National Institute for the Control of Vaccines and Biologicals (NICVB); and the General Department of Preventive Medicine (GDPM)	3	Vaccines (producing)

* Information is from the World Health Organization (https://www.who.int/publications/m/item/list-of-nras-operating-at-ml3-and-ml4).

tional regulatory authorities. The system should actively engage with bilateral and regional efforts to plan out where diagnostic, therapeutic, and vaccine dossiers may be submitted for approval, as part of broader coordination in moving medical products where they need to go.

Second, regional and multilateral development banks could agree that approval of a diagnostic, therapeutic, or vaccine by a WHO-listed authority with a given certification (e.g., maturity level 4) would be sufficient for them to extend loans for procuring that product. Banks' lack of internal guidance on criteria for loans and support and default dependence on the WHO's EUL designation exacerbated the bottleneck and access problems experienced during the Covid pandemic. The World Bank, for example, required either WHO prequalification and approval by one stringent regulatory authority or approval by three of those authorities in three regions.[5]

Expansion of regulatory pathways would prioritize public health by enabling diagnostics, therapeutics, and vaccines to reach populations sooner.

First, the WHO should not only provide technical benchmarking tools for regulatory assessment, but also undertake focused planning after national regulatory systems have achieved advanced levels of maturity. For example, as of October 2023, Korea, Saudi Arabia, and Singapore had achieved maturity level 4 designations, but now their regulators need to be integrated into a coordination initiative that identifies regional hubs for dossier review and approval during emergencies. Such integration could include memoranda of understanding between WHO-listed authorities and countries that are willing to accept their determinations for purposes of licensure and import during public health emergencies. These agreements could be developed under the auspices of regional organizations that already operate with cooperation from governments, such as the regional WHO offices, the Organization of Islamic Cooperation, or the Association of Southeast Asian Nations.

Third, as negotiators finalize a draft global pandemic agreement, provisions addressing regulatory strengthening could focus not only on national strengthening, but also on a coordinated and multilateral approach to leveraging regulatory capacity as it emerges. National regulatory capacity in Ghana, Egypt, Nigeria, South Africa, and Tanzania is stronger than that in many other African countries. Similarly, regulatory capacity in China, India, Indonesia, and Turkey is stronger than that in many other countries in their respective regions of Asia. With increased flexibility, countries and manufacturers could seek approval from these authorities. If applied with adequate precautions to continue ensuring safety and efficacy, this regulatory flexibility would allow low- and middle-income countries to obtain more vaccine doses earlier in a future pandemic response by means of pooled purchases. Decentralizing regulatory review could enable more timely assessment of medical products developed outside high-income countries. Reducing reliance on the WHO PQ program in this way would also ensure greater national control over vaccine supply and less reliance on a global entity such as COVAX (COVID-19 Vaccines Global Access) in low- and middle-income countries, many of which struggled with late deliveries and shortcomings in contract transparency and governance while participating in COVAX.

Expansion of regulatory pathways would prioritize public health by enabling diagnostics, therapeutics, and vaccines to reach populations sooner. By taking incremental but high-impact steps based on the WHO's classifications of regulatory systems, global health leaders can mount a more equitable and rapid response. Together, these steps can drive more cohesive responses to future public health emergencies.

Disclosure forms provided by the authors are available at NEJM.org.

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This article was published on August 3, 2024, at NEJM.org.

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DOI: 10.1056/NEJMp2406390

Collective Trauma and Commemoration — A Moment of Silence, Please

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Recent polls indicate that the majority of people in the United States believe the Covid-19 pandemic is over. Even as most people try to settle back into prepandemic routines, however, the startling toll of SARS-CoV-2 is still with us: nearly 1.2 million people in the United States have died from Covid-19, and one third of people report losing a close friend or relative. Rates of patient-reported general psychological distress, anxiety, and depression rose during the pandemic — to roughly 20 to 35%, according to pooled prevalence estimates.[1] It's unclear whether this distress will lead to an epidemic of psychiatric illnesses, such as major depression or anxiety disorders. But survey data show that grief and fear still linger for many people.

The pandemic had characteristics of a collective traumatic event. Collective trauma is a type of psychological harm caused by an overwhelming event that affects an entire group.[2] Our society faced an unprecedented threat that was ubiquitous and unpredictable, which undermined people's sense of safety. The frightening reality was one of global death caused by a mutating virus. Collective trauma can be viewed as a form of stress, though there is considerable debate about the likelihood that exposure to a given adverse experience will produce a traumatic response. Individual psychosocial and biologic factors undoubtedly play important roles in determining whether an adverse exposure will lead to trauma.[3]

Unlike more localized or time-limited catastrophic events that have caused trauma — such as specific mass shootings or the September 11 attacks — the Covid-19 pandemic represented a chronic, population-level stressor. And although many people can now breathe more easily, society still bears the emotional toll of the plague years. In assessing this toll, it's important to acknowledge that there was no singular experience of loss. Covid-19 had a disproportionate effect on members of marginalized racial and ethnic groups as well as on older people, essential workers, and people who were socially and economically disadvantaged and had limited access to health care.

Chronic stress can have adverse neurobiologic, psychological, and social consequences. Whereas acute stress responses rapidly and transiently mobilize glucose for energy and increase levels of norepinephrine, which can enhance focus and attention, prolonged exposure can have harmful effects.[4] Persistently elevated levels of norepinephrine and cortisol, which are typical of chronic stress, can increase the risk of anxiety and depression and impair neuronal function in the hippocampus and prefrontal cortex, thereby compromising cognitive abilities such as short-term memory and critical reasoning.

Exposure to a widespread threat over an extended period can also cause psychological reactions that may persist long after the danger has receded. During the pandemic, Americans were largely isolated from each other, and many were engulfed by grief. Normal gestures of care and love were dangerous. Moreover, the enemy was invisible and elusive. As the pandemic wore on, denial and other forms of defensiveness allowed some people to forget the source of the threat