Advancing Pandemic and Seasonal Influenza Vaccine Preparedness and Response: Harnessing Lessons from the Efforts Mitigating the COVID-19 Pandemic

Overview of the four consensus studies

Introduction

An estimated 1 billion people worldwide are infected by seasonal influenza every year, 3–5 million of whom suffer from severe cases, resulting in as many as 650,000 deaths[i, ii, iii]. Seasonal influenza causes billions of dollars of economic loss and strains health care systems annually[iv, v]. Influenza viruses are also highly contagious and constantly adapt and mutate, making influenza a high-risk respiratory illness with the potential for serious outbreaks each influenza season.

Beyond being a seasonal concern, influenza poses a pandemic threat. Influenza pandemics have occurred repeatedly throughout recorded history, devastating economies and health care systems. The 1918–19 influenza pandemic resulted in 50 million deaths, more than the death toll from World War I[vi]. Other influenza pandemics in 1957, 1968, and 2009 had lower death tolls but still severely impacted human health and the global economy. The economic burden of a moderate-to-severe influenza pandemic today would likely cost the global economy trillions of dollars[vii]. Despite the risks of seasonal and pandemic influenza, influenza vaccine preparedness is consistently met with complacency and is de-prioritized on health agendas and annual budgets by policymakers and public health officials.

Meanwhile, the global COVID-19 response has advanced vaccine research, development, manufacturing, distribution, and administration in unprecedented ways. This pandemic has challenged the way the global community views vaccine and pandemic preparedness. The four consensus studies that are part of this series state that the world must learn from this experience to avoid circumstances similar to or worse than COVID-19, and to finally see preparedness as a muscle that we must strengthen, rather than neglect, during interpandemic times.

The consensus studies acknowledge that addressing seasonal and pandemic influenza preparedness is an essential priority for improving our global preparedness muscle. After all, it is widely believed[viii] that the potential for another major influenza pandemic is more a matter of "when" than "if". The consensus study findings agree that the time is now to seize this moment and strengthen preparedness for seasonal and pandemic influenza by building on the lessons learned from the COVID-19 pandemic and existing influenza programs. If the global community does not act on this critical opportunity, we run the risk of being yet again unprepared for the next pandemic threat.

The Advancing Pandemic and Seasonal Influenza Vaccine Preparedness and Response Initiative (the Initiative), managed by the National Academy of Medicine with funding from the U.S. Department of Health and Human Services (HHS) Office of Global Affairs, developed four consensus studies to explore how the scientific and technical breakthroughs from the COVID-19 pandemic could advance pandemic and seasonal influenza preparedness and response. Written by four independent committees comprised of international experts, these reports highlight why the global community needs to act immediately, comprehensively, and strategically to mitigate future threats from seasonal and pandemic influenza.

Report Highlights

Vaccine Research and Development to Advance Pandemic and Seasonal Influenza Preparedness and Response: Lessons from COVID-19

This report provides recommendations on how to leverage knowledge gained from the COVID-19 pandemic to develop improved influenza vaccines, identify new and improved vaccine platforms, improve regulatory practices for a pandemic scenario, and expand and improve manufacturing capacity.

The committee concluded that novel vaccine platforms have the potential to improve the effectiveness and speed with which influenza vaccines are produced, but significant R&D funding is necessary to develop those novel platforms and technologies. Innovations in vaccine technology driven by COVID-19 will also require building new production capacity. In addition to basic and translational science, clinical science for influenza vaccine testing should expand, especially into low- and middle-income countries (LMICs) to fill the clinical funding gap, to decrease the risk associated with the large investments necessary for clinical development, and to better meet the needs of diverse populations.

The committee also recommended self-sustaining expansion of vaccine manufacturing capacity in LMICs to avoid delayed rollout of vaccines and limit the spread of viral variants. Financial aid to vaccine manufacturers could incentivize riskier infrastructure investments, and the public sector should support data-sharing infrastructure to further encourage this expansion. Finally, the committee concluded that regulators should develop comprehensive and transparent guidelines for how to conduct preclinical and early clinical trials between pandemics, and develop pathways for rapid review of vaccines for pandemic strains.

Globally Resilient Supply Chains for Seasonal and Pandemic Influenza Vaccines

This report provides recommendations on how to bolster the global supply chain for pandemic and seasonal influenza, focused on vaccine manufacturing and distribution, research and development, manufacturing inputs, and indemnity.

The committee concluded that a well-coordinated global body with an inclusive governance structure could orchestrate a globally distributed supply chain to produce influenza vaccines, as every component necessary for global vaccine manufacturing must be defined, identified, and managed to ensure the equitable supply of seasonal and pandemic influenza vaccines. Countries also need access to a balanced portfolio of vaccines suitable for different country contexts, and better data-driven tools for supply and demand planning, to account for the logistical demands of transporting and disseminating vaccines.

Countries need high-quality, robust, and actionable pandemic preparedness plans that are periodically updated and prioritize harmonization and collaboration on strategies across multiple stakeholder groups. Finally, the committee recommended financial incentives for developing vaccines to increase the demand for influenza vaccines and improve the return on investment, and improved guidelines to streamline regulatory pathways for approval, especially for novel vaccine platforms.

Public Health Lessons for Non-Vaccine Influenza Interventions: Looking Past COVID-19

This report provides recommendations on how individual and government-level public health interventions and countermeasures can be used to mitigate the spread and effects of influenza both before and after vaccines are available based on lessons learned from COVID-19 response.

The committee concluded that preparedness efforts should include investments to expand holistic surveillance strategies including a One Health approach to considering circulating and emerging viruses, to improve data collection accuracy and harmonization, and to research the effectiveness of non-vaccine countermeasures. Preparedness measures should also include stockpiling drugs with proven safety and potential effectiveness against respiratory viruses.

Before – and even after – vaccines are developed, public health control measures are effective means of responding to future seasonal and pandemic influenza events. Response efforts should deploy a combination of harm-minimizing measures with rigorous data collection and monitoring. Preparation for clinical trials should include establishing international adaptive trial platforms, which will permit rapid and rigorous research to compare the effectiveness of therapeutics, individually and in combination.

Countering the Pandemic Threat through Global Coordination on Vaccines: The Influenza Imperative

This report provides recommendations on how to identify and overcome barriers to effective global coordination and sustainable financing for pandemic and seasonal influenza preparedness and response, drawing on successes and challenges from the global response to COVID-19.

The committee concluded that draws seven overarching recommendations for how the urgent influenza threat – the "influenza imperative" – should be conceptualized and prioritized as a crucial component of future PPR. The recommendations include aligning governance and coordination for pandemic preparedness and response for respiratory pathogens with pandemic potential, financing an integrated and modern respiratory virus surveillance system, examining the limitations and potential of the PIP Framework and Nagoya Protocol for pathogen sharing, utilizing public-private partnerships to accelerate vaccine development, financing and organizing a vaccine moonshot to identify a universal influenza vaccine, supporting manufacturing scale-up and geographically distributed hubs for influenza vaccine manufacturing, and generating influenza vaccine demand through globally coordinated deployment activities. Given the many organizations with mandates for influenza and an evolving PPR landscape during 2021, many recommendations are targeted at the G7 and G20's proposed PPR structures. The committee acknowledges that many other multilateral, bilateral, and civil society actors beyond the G7 and G20 are vital for the implementation of these recommendations.

References

[i] Palache, A., A. Abelin, R. Hollingsworth, W. Cracknell, C. Jacobs, T. Tsai, and P. Barbosa. 2017. Survey of distribution of seasonal influenza vaccine doses in 201 countries (2004–2015): The 2003 world health assembly resolution on seasonal influenza vaccination coverage and the 2009 influenza pandemic have had very little impact on improving influenza control and pandemic preparedness. Vaccine 35(36):4681–4686.

[ii] Iuliano, A. D., K. M. Roguski, H. H. Chang, D. J. Muscatello, R. Palekar, S. Tempia, C. Cohen, J. M. Gran, D. Schanzer, B. J. Cowling, P. Wu, J. Kyncl, L. W. Ang, M. Park, M. Redlberger-Fritz, H. Yu, L. Espenhain, A. Krishnan, G. Emukule, L. van Asten, S. Pereira da Silva, S. Aungkulanon, U. Buchholz, M. A. Widdowson, and J. S. Bresee. 2018. Estimates of global seasonal influenza-associated respiratory mortality: A modelling study. Lancet 391(10127):1285–1300.

[iii] WHO. 2018. Ask the expert: Influenza q&a. (accessed April 7, 2021).

[iv] Iuliano et al., 2018.

[v] Putri, W. C. W. S., D. J. Muscatello, M. S. Stockwell, and A. T. Newall. 2018. Economic burden of seasonal influenza in the united states. Vaccine 36(27):3960–3966.

[vi] Taubenberger, J. and D. Morens. 2006. 1918 Influenza: the mother of all pandemics. Emerging Infectious Diseases 12(1):15–22.

[vii] GPMB (Global Preparedness Monitoring Board). 2019. A world at risk: Annual report on global preparedness for health emergencies. World Health Organization. Geneva, Switzerland.

[viii] Kelland, K. 2019. World must prepare for inevitable next flu pandemic, WHO says. Reuters (accessed August 19, 2021).

Complete List of Recommendations

Vaccine Research and Development to Advance Pandemic and Seasonal Influenza Preparedness and Response: Lessons from COVID-19

2.1: The U.S. Department of Health and Human Services, through the National Institute of Allergy and Infectious Diseases, the Biomedical Advanced Research and Development Authority, and the U.S. Department of Defense, as well as other corresponding governmental and funding agencies domestically and abroad, should invest, proportionate to the enormous costs of pandemics, in basic and translational research to reveal a diverse array of influenza vaccines, using different platforms, viral targets, adjuvants, and delivery systems. This will allow selection of the candidates most fit for purpose to be brought to authorization and sufficient production and distribution to optimize the control of influenza across diverse settings and phases of pandemics and epidemics.

2.2: The World Health Organization should advocate and coordinate with multilateral stakeholders (e.g., the Coalition for Epidemic Preparedness Innovations), governments, funding agencies, the vaccine industry, and philanthropic organizations to build global capacity for robust and internationally comparable preclinical, clinical, and immunological assessments of influenza vaccine candidates, including novel candidates that use innovative structures, targets, and delivery systems to potentially broaden or improve protection.

2.3: International research networks (e.g., the National Institutes of Health/U.S. Centers for Disease Control and Prevention funding networks) supported by governments and funding agencies, the World Health Organization, and the vaccine industry should support, carefully plan, and conduct multi-center international clinical trials and field studies to compare emerging vaccines with standard vaccines in, among others, geographically, demographically, and immunologically diverse populations to inform rational and situation-based use and manufacture of an extended array of vaccines.

2.4: National regulators should engage with the vaccine industry and academic researchers in the development, standardization, and implementation of innovative assays to evaluate vaccines that induce immunity through mechanisms other than strain-specific neutralizing hemagglutination inhibiting antibodies in order to reach consensus on the validation of these assays that will allow approval or licensure of influenza vaccines based on a broader range of assays that reflect induction of immunity.

3.1: The World Health Organization, in collaboration with national public health agencies (e.g., the U.S. Centers for Disease Control and Prevention, the European Centre for Disease Prevention and Control, the China Center for Disease Control and Prevention, and the Africa Centres for Disease Control and Prevention) should conduct burden-of-disease studies in low- and middle-income countries to understand factors such as the health and economic burden of influenza illness and barriers to immunization in adult, pregnant, and pediatric populations to ensure development of infrastructure and capacity needed for pandemic vaccine development and implementation. Cost-benefit analyses should include additional economic productivity losses caused by delayed access to a vaccine in a pandemic.

3.2: The International Coalition of Medicines Regulatory Authorities and the World Health Organization, in partnership with national regulatory (e.g., the U.S. Food and Drug Administration and the European Medicines Agency) and public health agencies (e.g., the U.S. Centers for Disease Control and Prevention, the European Centre for Disease Prevention and Control, the China Center for Disease Control and Prevention, and the Africa Centres for Disease Control and Prevention) should invest, on a global level, in data infrastructure and capacity building to conduct real-time sentinel site surveillance of vaccine safety and effectiveness of different vaccine products deployed for use in epidemics and pandemics in diverse populations (e.g., age group, gender, race/ethnicity, geographic, presence of comorbidities, pregnancy, and socioeconomics), including a plan to ensure coordination, collaboration, and data sharing across these sentinel surveillance sites.

3.3: The International Coalition of Medicines Regulatory Authorities and the World Health Organization (Global Advisory Committee on Vaccine Safety) should ensure international coordination and collaboration on the timely and transparent review of vaccine safety data during epidemics and pandemics to support real-time decision making about the use of vaccines. Safety data should be made available to support country-level benefit-risk assessments, particularly for low- and middle-income countries relying on regional data from sentinel sites conducting safety surveillance.

4.1: The U.S. Department of Health and Human Services and the World Health Organization should develop a plan for a sufficient and self-sustainable global supply of influenza vaccines for pandemics. This includes

- Convening, supporting, and encouraging multi-national, public, and private vaccine manufacturers to benchmark, prioritize, and harmonize influenza vaccine manufacturing; and
- Enhancing and expanding support of the global influenza vaccine manufacturing network, creating manufacturing hubs for greater collaboration, and building capacity to address challenges in manufacturing in low- and middle-income countries.

4.2: Vaccine manufacturers should take a risk-based approach to pandemic influenza preparedness. This approach would be most effective if incentivized, and could include

- Participating during research and development, data sharing, technology adoption, and training activities with international partners;
- Expanding internal capacity to assess the production needs and their risks;
- Using scientific evidence to design strategies to reduce risks (e.g., World Health Organization prequalification, licensing, and marketing); and
- Formalizing technology transfer (scale-up and scale-out) activities taking into consideration time lines and the outcomes for equitable costs, access, and distribution.

5.1: The U.S. Food and Drug Administration and other national regulators (e.g., European Medicines Agency) working with the scientific community and pharmaceutical industry should enhance comprehensive guidance for the development of influenza vaccines on novel platforms through emergency use authorization to full licensure. This guidance should provide pathways for seasonal and pandemic influenza.

5.2: The U.S. Food and Drug Administration and other national regulators (e.g., European Medicines Agency) should commit to transparency in the oversight of clinical trials, review of data, authorization, and approval of pandemic influenza vaccines, including the release of facility inspection findings, clinical trial protocols, and clinical data that are the basis of decision making. Regulators should convene independent advisory committees to systematically review data, make recommendations, and build public understanding and confidence prior to the authorization or approval of novel vaccines.

5.3: The World Health Organization and the International Coalition of Medicines Regulatory Authorities should encourage and support the coordination between regulatory and public health agencies (e.g., the U.S. Centers for Disease Control and Prevention, the European Centre for Disease Prevention and Control, the China Center for Disease Control and Prevention, and the Africa Centres for Disease Control and Prevention) when announcing different decisions on the same or similar vaccines, to explain the different underlying circumstances and judgments.

5.4: Vaccine manufacturers should adopt a code of conduct for press releases and other communications regarding vaccine trial results and other matters that emphasizes the critical role of regulatory review.

Globally Resilient Supply Chains for Seasonal and Pandemic Influenza Vaccines

3.1: HHS and WHO should develop a plan for a sufficient and self-sustainable global supply of influenza vaccines for pandemics, including (1) convening, supporting, and encouraging multinational, public and private vaccine manufacturers to benchmark, prioritize, and harmonize influenza vaccine manufacturing, and (2) enhancing and expanding support of the global influenza vaccine manufacturing network, creating manufacturing hubs for greater collaboration, and building capacity to address challenges in manufacturing in LMICs.

3.1a: The G20 should commission an independent panel of manufacturing and supply chain experts to conduct a review of the technical capabilities and governance structure of the COVAX Manufacturing Task Force to extract lessons learned, assess its suitability for pandemic influenza, and inform the design of the structure, management, and governance of the committee's recommended task force.

3.1b: U.S. government entities, including the Department of Health and Human Services and its agencies (such as the Food and Drug Administration, the Biomedical Advanced Research and Development Authority, and the Centers for Disease Control and Prevention), the U.S. Trade Representative, the Department of Commerce, the U.S. Agency for International Development, and others should work collaboratively with the committee's recommended task force in specific areas and, as identified in this report, take a global leadership role in activities under the task force.

3.2: The Office of the Secretary of the Department of Health and Human Services (HHS) and its technical agencies (including the Office of Global Affairs, the Assistant Secretary for Preparedness and Response, and the Biomedical Advanced Research and Development Authority), in collaboration with appropriate global technical counterparts, should provide technical and resourcing support to the committee's recommended task force (see Recommendation 3-1) to develop a comprehensive pandemic preparedness and response capability framework that comprises three elements:

- End-to-end visibility of critical inputs: in collaboration with the World Trade Organization, the Coalition for Epidemic Preparedness Innovations, the Developing Countries Vaccine Manufacturers Network, and the International Federation of Pharmaceutical Manufacturers & Associations, evaluate a means to define, identify, and track (e.g., through barcodes and blockchain technologies) the global real-time availability of potentially supply-constrained critical inputs necessary to manufacture vaccines for pandemic influenza, known as the essential global commons list for pandemic influenza vaccine manufacturing.
- Resiliency assessment and analysis: in collaboration with other U.S. agencies (including the Office of Science and Technology Policy, the U.S. Trade Representative, and the U.S. Agency for International Development) provide technical and resourcing support for the committee's recommended task force to forecast supply and demand of critical inputs, including workforce personnel and training needs for pandemic influenza vaccine manufacturing, and perform a resiliency assessment of the current end-to-end network to identify vulnerabilities in physical inputs, as well workforce gaps, that may impede pandemic influenza vaccine manufacturing.
- Preparedness, response, and global coordination: working with the U.S. Department of State, coordinate efforts both within HHS and across other U.S. government entities to provide technical and resourcing support to the committee's recommended task force to develop technical capabilities to ensure sourcing, production, distribution, risk management, and coordination of critical components necessary for manufacturing seasonal and pandemic influenza vaccines, including capabilities to ensure globally effective preparedness and response.

3.3: The U.S. Food and Drug Administration and the regulatory arm of the World Health Organization (WHO) should evaluate the development of fast turnaround batch release (including potency and stability-indicating) assays for seasonal and pandemic influenza vaccine manufacturing and ready global access to international reference standards and benchmark comparators (e.g., immunological reagents) for use in product analytics and clinical trials. The WHO Collaborating Centers for Influenza should facilitate the development of internationally harmonized and prioritized assays acceptable to regulatory bodies. A long-term goal should be set to achieve global regulatory harmonization and convergence of the analytical standards and assays, in partnership with the International Coalition of Medicines Regulatory Authorities.

3.4: Improving vaccine manufacturing workforce development and capacity should be prioritized by relevant global stakeholders:

- Government agencies, commercial entities, nongovernmental organizations, and academic institutions with the requisite knowledge and skill sets should partner with advanced and developing vaccine manufacturers to develop vaccine manufacturing and development technology hubs.
- The Department of Health and Human Services and its technical agencies, including the Office of Global Affairs, with nongovernmental partners, such as PATH, should develop and implement a medical countermeasure "university" for training a vaccine manufacturing and delivery critical workforce.

3.5: The Office of Global Affairs, in coordination with other U.S. interagency stakeholders and working closely with global agencies, such as the World Health Organization, should provide technical and resourcing support to the committee's recommended task force to evaluate the feasibility, structure, and sustainability of a globally distributed network of regional and local vaccine manufacturing capacity.

4.1: The U.S. Department of Health and Human Services (HHS), in partnership with its counterparts in other countries and relevant global stakeholders and funders, should ensure a systems approach to the design and development of vaccines for feasible distribution and delivery in various global contexts and support relevant innovations.

- **4.1(a)**: HHS, its global counterparts, and relevant global funders and stakeholders should encourage attention to operational considerations up-front when funding vaccine development.
- **4.1(b)**: The Food and Drug Administration (FDA), along with the World Health Organization (WHO), should encourage manufacturers to consider including WHO's preferred characteristics in their submissions for clinical trials. The National Institutes of Health (NIH) should prioritize including these preferred characteristics in its influenza vaccine research program.
- **4.1(c)**: HHS offices and relevant agencies, including the Assistant Secretary for Preparedness and Response and NIH, should make sustained global investments in novel vaccine end-to-end technologies, including stabilization and delivery platforms, that will improve equitable access and adaptation for vaccines to be used in various temperature settings.
- **4.1(d)**: WHO and FDA, after issuance of a WHO emergency use listing procedure or an FDA emergency use authorization, should require digital packaging labels during a pandemic so that changes in vaccine stability and shelf life can be immediately understood and easily accessed by end-users. These labels could also serve as a verification mechanism against counterfeit vaccines.

4.2: The World Health Organization, its partners, and its funders should facilitate a global vaccine portfolio rollout to ensure the development and access to a broad portfolio of influenza vaccines.

4.3: The Centers for Disease Control and Prevention should work with the World Health Organization, Gavi, and global counterparts to commission studies in demand forecasting and demand uptake. The National Vaccine Advisory Committee should be augmented to engage in this task.

4.4: The Centers for Disease Control and Prevention and the National Institutes of Health should support the development of better models for influenza vaccine cost effectiveness. The U.S. Agency for International Development should support technical assistance to strengthen country systems for vaccine uptake.

4.5: The Office of Global Affairs, in partnership with the World Health Organization, Gavi, UNICEF, and relevant global funders, should facilitate the development of global tools to help countries with better supply planning for vaccines and ancillary supplies planning, allocation, and rollout decisions, and with obtaining necessary funding for operations.

5.1: The Office of Global Affairs, with other agencies in the Department of Health and Human Services and with the Expert Committee on Influenza of the World Health Organization, along with other global stakeholders, should periodically convene to identify the challenges in global preparedness for influenza, as well as overall preparedness for emerging pathogens, benefiting from the lessons learned from recent disease outbreaks to address global supply challenges, and support cold chain infrastructure needs across the temperature spectrum, as well as to plan mock drills and tabletop exercises to test these systems. The outcome of these meetings should inform national authorities on approaches and best practices to prepare and periodically update their national preparedness plans, with technical support from different agencies, so that the resulting plans are high quality, granular, relevant, and actionable. National authorities should be encouraged to engage with the private sector for pandemic preparedness and response.

5.2: The World Health Organization, the Coalition for Epidemic Preparedness Innovations, UNICEF, and Gavi, along with other stakeholders and key regional structures, using lessons learned from the rollout of COVID-19 vaccines, should review, update, adapt, and harmonize all developed and innovative COVID-19 vaccine access tools to improve future influenza outbreak responses. Appropriate training curricula and tools that emphasize systems thinking and medical logistics should be included.

5.3: The World Health Organization, working with relevant partners, such as the Coalition for Epidemic Preparedness Innovations, UNICEF, and Gavi, should support the development of a global influenza vaccine supply and demand planning tool. The tool should be linked or aligned to allow real-time consolidation of relevant global data to inform manufacturing and accuracy of supply and demand status to better inform allocation and avoid wastage.

5.4: An independent convening group (such as Chatham House, the Rockefeller Foundation, or the ASPEN Institute) should convene a workshop for global health technical agencies—including the World Health Organization, the Coalition for Epidemic Preparedness Innovations, UNICEF, and Gavi; international financial institutions, such as the World Bank and the International Monetary Fund; other development financial institutions; and regional organizations, such as the African Union and the Pan-American Health Organization— to share updates from evaluating the tools used to respond to the COVID-19 vaccine rollout, identify current capabilities, constraints, and gaps, and aim to harmonize country assessment methodologies relevant for different stakeholders.

5.5: The United States and international agencies should develop mechanisms to evaluate pandemic preparedness plans and financing mechanisms to support their development, while incentivizing country compliance. Specifically:

- The U.S. Congress should authorize government agencies and programs, such as the U.S. Agency for International Development and the President's Emergency Plan for AIDS Relief, to include pandemic preparedness as an input into country funding proposals for various health programs and provide financial support and technical assistance if deficiencies in pandemic preparedness plans are uncovered.
- Global institutions, including G20, the World Bank, the International Monetary Fund, and the International Finance Corporation, and regional multilateral development banks should integrate country preparedness assessments into their country economic assistance programs, such as development assistance, loans, and grants, and they should advocate for financial support. They should also identify gaps in country preparedness and develop and evaluate pandemic preparedness and response plans.

5.6: The United States and international agencies (including the World Health Organization, the World Bank, and the International Monetary Fund), along with regional bodies (such as the Africa Centers for Disease Control and Prevention and the Pan- American Health Organization), should support the development of regional structures with appropriate expertise to assist countries in the region to develop pandemic preparedness plans and ensure plan quality and compliance.

5.7: The G20 should ensure up-front regional engagement in a future organizational structure for the financing, procurement, and deployment of pandemic vaccines to ensure the inclusion of access to vaccines for their regions.

5.8: The Department of Health and Human Services should fund a comprehensive review of innovations developed and deployed during the COVID-19 pandemic, carried out by an independent scientific body. The review should cover such critical areas as regulatory approval, manufacturing, global and in-country distribution, delivery, and lessons learned, and it should identify innovation gaps for future pandemic preparedness and response.

6.1: The World Health Organization, in collaboration with the Coalition for Epidemic Preparedness Innovations, PATH, the Food and Drug Administration, and the Biomedical Advanced Research and Development Authority, should conduct a comparative assessment of all available and potential manufacturing technologies for influenza vaccines. Metrics for assessment should include speed, complexity, scalability, flexibility to address alternative diseases, efficiency, and potential for mass production. The assessment should inform a decision-making framework for future investments that recognizes the dynamically evolving nature of technologies and tradeoffs for different platforms.

6.2: Public funders of vaccine development for influenza viruses of pandemic potential, including the Department of Health and Human Services, should ensure that contracts and awards to biotechnology innovator grantees stipulate, in detail, their proposed mechanism to scale up production, which could include partnership with a large proven and experienced vaccine development and manufacturing company.

6.3(a): The G20 should provide substantial monetary and other incentives—such as intellectual property voluntary licensing, advanced market commitments, and priority review vouchers—administered through a future structure for financing, procurement, and deployment for pandemic vaccines, to develop improved seasonal and pandemic influenza vaccines that would increase uptake and demand, leading to sustainable manufacturing capacity investments. These incentive mechanisms should set clear expectations of manufacturers to leverage their innovations to respond during pandemics.

6.3(b): The U.S. International Development Finance Corporation and the U.S. Agency for International Development should provide concessional capital and technical assistance to manufacturers in developing countries to begin producing improved seasonal and pandemic influenza vaccines.

6.4: The World Bank should develop a global indemnification mechanism that can be applied to all vaccines with World Health Organization (WHO) emergency use listing or prequalification, regardless of the mechanism (pooled or bilateral) or financing used to procure the vaccines.

6.5(a): The Department of Health and Human Services and the Food and Drug Administration should investigate the barriers to public transparency of vaccine clinical trial protocols during a public health emergency and evaluate measures, including legislation, to remove these barriers..

6.5(b): The World Health Organization should support an independent after-action review of its emergency use listing procedures, including learning from the COVID-19 experience, to make recommendations regarding appropriate process structure, staffing, and resourcing for surge capacity needed for expedited reviews during a future pandemic.

6.5(c): The Department of Health and Human Services, along with the World Health Organization, should support the creation of a network of inspectors to conduct rapid inspections of vaccine manufacturing plants during a pandemic to ensure vaccine quality, which may include providers of assays, technical experts, and lot comparability in secondary manufacturing

Public Health Lessons for Non-Vaccine Influenza Interventions: Looking Past COVID-19

2.1: The World Health Organization, the World Bank, and regional public health organizations should work collaboratively with countries (particularly for low- and middle-income countries and those with extensive animal-human interfaces) to build sustainable capacity for routine surveillance in animals (wildlife, livestock, and domestic), and develop and support interagency One Health platforms.

2.2: Countries should institute surveillance as the backbone of their health care systems, which should include submitting aggregated clinical data feeding into public health agencies. To ensure that policy makers have access to accurate, timely, and comprehensive risk assessments, national authorities—with the advice and assistance of regional and global public health agencies—should establish more robust surveillance systems, involving public hospitals and academic medical centers, manufacturers of diagnostics, and social network platforms. Epidemiologists should be alert to potential ascertainment biases regarding sampling frames and other methodological pitfalls, account for such biases during analysis and interpretation of the data and should notify authorities to take these biases into account and seek support for improving surveillance methods to better achieve representativeness and sufficient geographical coverage.

2.3: National public health agencies should both strengthen the capabilities of local and provincial authorities to accurately, rapidly, and transparently report data about novel agents and strains and improve their own reporting of data to such regional organizations and global bodies as the World Health Organization and the One Health Tripartite. The global bodies should develop methods to harmonize data from multiple sources, to enable prompt dissemination of useful, comprehensive data, especially to the national and regional organizations that have contributed to the data pool. Organizations to which data are submitted at all levels should work toward removing barriers and disincentives to making full and accurate reports.

2.4: The World Health Organization and regional disease control agencies (e.g., European Centre for Disease Prevention and Control, Africa Centres for Disease Control and Prevention) should work with countries, and national governments should work with subnational entities (counties, states, provinces), to harmonize, coordinate, and optimize surveillance activities, data collection, and sharing.

3.1: The World Health Assembly should amend the International Health Regulations to allow countries to use border measures during a pandemic of influenza or other respiratory viruses.

3.2: The World Health Assembly should amend the International Health Regulations to allow countries to use border measures during a pandemic of influenza or other respiratory viruses.

3.3: In collaboration with other expert bodies, the World Health Organization (WHO) should develop and disseminate technical recommendations on how to assess and create ventilation conditions in various settings that will reduce transmission of respiratory viruses in various settings. WHO and its collaborators should promote these widely and assist countries in incorporating them into their building standards and implementing them between pandemics.

3.4: The World Health Organization—as well as national centers for disease control and prevention and other regional, national, and subnational public health authorities—should recommend against the installation of clear plastic or other similar barriers and face shields without appropriate face masks.

3.5: Funders should incentivize more integration of research among scientific and medical fields to inform investigations of transmission, prevention, and treatment of influenza and other respiratory viruses. Such integration should include a standardizing and sharing of language across sectors, and mechanisms for sharing relevant data.

4.1: Global and regional public health agencies (e.g., World Health Organization, Pan American Health Organization, Africa Centres for Disease Control and Prevention) and national governments, including their local and state health agencies, should adopt policies that are tailored to each affected population, taking into account its social, economic and cultural characteristics, needs and resources, and other contextual factors, including norms, values and beliefs, in order to optimize the implementation of public health interventions, especially those that rely on individual behaviors.

4.2: Governments, leaders of departments of health at local, state, and national levels, and elected and appointed government leaders should:

- Take the systemic factors, such as race and socioeconomic disadvantages that affect the health of affected populations into consideration and leverage behavioral health research and marketing tactics when developing and implementing public health interventions;
- Demonstrate, in their behavior, adherence to non-vaccine measures to prevent influenza in order to promote public trust in, and uptake of these measures;
- Engage the community—including grassroots organizations, spiritual leaders, teachers, and sports coaches—in making and communication decisions about public health measures; and
- Choose words to convey communications positively (e.g., “physical distancing,” “social solidarity,” and “stay at home” rather than “social distancing,” “individual isolation,” and “lockdown”).

4.3: Funding agencies should create mechanisms to support the rapid application of data and implementation frameworks during an influenza pandemic as well as to enhance similar mechanisms during interepidemic periods. Such mechanisms can be used to support implementation research on non-vaccine control measures for influenza.

4.4: National governments—as well as local, state, and global public health agencies—should develop readily implementable intervention plans for outbreaks of influenza and other diseases. Such plans should specify how, from the beginning of an outbreak, the government will

- Take into consideration the needs of the population affected, with special attention to the needs of marginalized groups;
- Iteratively collect and use data about the implementation and effectiveness of non-vaccine control measures to adapt plans where needed; and
- Use proven scientific frameworks to guide and improve such measures.

5.1: National governments should mandate that the appropriate authorities (ministries of health or comparable government agencies):

- Regularly evaluate existing stockpiles of therapeutics (including antivirals, other antimicrobials for treatment of secondary infection, and supportive care treatments, such as oxygen) and other articles needed for care delivery (e.g., personal protective equipment);
- Secure sources that can reliably supply all items needed during an influenza pandemic; and
- Assess, and establish where possible, local production capabilities for all such items.

5.2: The government agencies responsible for public health guidance in each country (e.g., United Kingdom Health Security Agency, U.S. Centers for Disease Control and Prevention) should develop a framework to guide the use and prioritization of treatments that can be flexible with changing evidence during a respiratory viral pandemic. That framework should be able to be adjusted depending on the pathogen, taking into account its transmission route, the at-risk populations, and associated morbidity and mortality rates. The framework should identify:

- Who will evaluate guidance from global and national health organizations and from professional societies in order to define evidence-based treatment guidelines;
- How guidelines for treatment selection and delivery will be communicated to health agencies in the country's states/provinces/ regions and to frontline health care facilities, with a focus on avoiding the use of non-evidence-based therapeutics outside of clinical trials;
- How suitable places to administer care will be selected, with consideration of options that provide alternatives for care delivery outside of already overwhelmed health facilities and primary care clinics;
- Which populations should be the focus for therapeutic delivery with scarce resource availability (e.g., prevention in those not yet infected, versus treatment of those who are mildly or critically ill), who will make those determinations, and how community interests will be incorporated; and
- How to distribute a treatment modality equitably throughout the country and among patients including when health systems have moved to crisis standards of care because the available resources have become inadequate to meet the needs of all patients.

5.3: Global (World Health Organization) and regional (e.g., African Centres for Disease Control and Prevention, European Centre for Disease Prevention and Control, Pan American Health Organization) health organizations should collaborate to determine how therapeutics and the resources needed for their delivery can be shared among countries to ensure equitable distribution and reduce or slow the spread of the pandemic.

5.4: Intergovernmental organizations, government agencies, foundations, pharmaceutical and biotechnology companies, universities, and research institutes should focus their efforts on research strategies and platforms that were shown to be particularly effective during the COVID-19 pandemic: screening potential antiviral drugs for safety and efficacy; evaluating therapeutic approaches that target host responses in addition to the viruses themselves; developing and maintaining national and international research collaboratives; and building the capacity for rapid adaptive therapeutic evaluation during a pandemic to inform evidence-based treatment guidelines.

Countering the Pandemic Threat Through Global Coordination on Vaccines: The Influenza Imperative

1: WHO should develop an integrated agenda to strengthen preparedness and response for all respiratory pathogens of pandemic potential, which includes surveillance, information sharing, and the development, manufacturing, and deployment of vaccines and other essential components of the vaccine manufacturing supply chain. This agenda should comprise a key component of the overarching agenda for pandemic preparedness and response, encompass pandemic influenza, and build on existing mechanisms for coordination in the influenza arena. To accomplish this, member states should task WHO to do the following:

- **(a).** Assume leadership for this agenda and, with collaboration from relevant multilateral partners (e.g., the Food and Agriculture Organization [FAO] and World Organization for Animal Health [OIE]), propose a framework for strengthened surveillance systems and information sharing at country, regional, and global levels, to ensure rapid detection of new threats and to enable swift dissemination of information essential to accelerated vaccine development.
- **(b).** Work jointly with existing international and stakeholder organizations with expertise in vaccine R&D, manufacturing coordination and supply chain management, and deployment (e.g., the Coalition for Epidemic Preparedness Innovations [CEPI], the United Nations Children's Emergency Fund [UNICEF] and Gavi, the Vaccine Alliance), to develop, in consultation with vaccine manufacturers, a framework for improved global coordination of vaccine development, production, and deployment for respiratory pathogens with pandemic potential, which includes defined roles, responsibilities, and accountability structures.

2: With urgency (over the next 3-5 years), the G7 and G20 should ensure that increased investments are made in surveillance systems for pathogens with pandemic potential, which support and encompass every country and region, by doing the following:

- **(a).** Creating incentives, structures, and pathways for key stakeholders to develop and implement integrated surveillance, which should include firmer support for zoonotic surveillance in the framework of One Health programs, such as through WHO/ OIE/FAO stakeholders.
- **(b).** Strengthening and financing regional surveillance structures and networks through partnerships between regional development banks and organizations. For example, in the South Asia and Southeast Asia regions this could be accomplished in conjunction with the Association of Southeast Asian Nations (ASEAN), Asian Development Bank (ADB), and Asian Infrastructure Investment Bank [AIIB], and in the Middle East and North Africa with the Organization of Islamic Cooperation (OIC), Gulf Cooperation Council, and Islamic Development Bank (ISDB).
- **(c).** Ensuring that the financing mechanism selected by the G7/G20 for PPR more broadly includes sustainable funding for surveillance and that this pooled funding is sufficient to enable surveillance for respiratory pathogens, especially encompassing those with pandemic potential, at the national and regional levels.
- **(d).** This global funding mechanism's governance should include relevant international agencies, such as the International Fund for Agricultural Development (IFAD), OIE, FAO, and World Food Program (WFP), in addition to multilateral and regional development banks and the WHO.

3: The World Health Assembly (WHA) should explicitly clarify that the PIP Framework covers genetic sequence data. The WHA should also use established PIP Framework principles as a foundation for future WHO member state agreements, or advocate for their use in agreements negotiated by other international organizations, so that the access and benefit and information-sharing principles cover a broader range of pathogens and their genetic sequence data. To accomplish this, the WHA should, with support of the United Nations, do the following:

- **(a).** Establish accountability and compliance monitoring for member states and other parties in the PIP Framework and future agreements on access and benefit sharing through regular reviews and meetings of member states, and by building or strengthening norms and holding leaders accountable for following through on commitments.
- **(b).** Incorporate the principles of equity, shared accountability, and multilateralism in any future pandemic treaty or instrument and ensure that the surveillance systems that can rapidly detect, assess, report, and share these viruses are publicly recognized to be a global public good.
- **(c).** Develop a mechanism for countries to share viruses openly and rapidly, including their genetic sequences and other essential supporting laboratory information and epidemiological data for both risk assessment and risk management (developing vaccines, therapeutics, and diagnostics), while setting up incentives for industry and member states to share benefits and products (vaccines, therapeutics, and diagnostics), and to facilitate transferring technology. This requires a recognition of the concerns of industry over intellectual property. This mechanism should include regular public reporting as part of a transparency and monitoring system to hold countries and governments accountable for their level of pandemic preparedness and response.
- **(d).** Request that the WHO secretariat approach the Convention on Biological Diversity (CBD) secretariat to initiate a process for a new international agreement or instrument to be established as a "special international instrument" under Article 4.4 of the Nagoya Protocol (allowing the agreement to bypass some Nagoya Protocol requirements while remaining consistent with its objectives). The new international agreement or instrument could either be negotiated as an additional protocol to the CBD alongside the Nagoya Protocol, be a component of a possible future pandemic treaty, or be negotiated within WHO as a new ad hoc international agreement. The special international instrument should address the sharing of genetic sequence data and other necessary information, such as important epidemiological and laboratory data, in addition to the pathogen samples. The Meeting of the Parties to the Nagoya Protocol, in collaboration with WHO, should recommend that Parties to the Protocol facilitate and streamline national implementation procedures to facilitate the timely international sharing of pathogens in line with the urgency of responding to an outbreak. The Meeting should also acknowledge that genetic sequences of both human and animal pathogens are essential for modern science to adequately assess and respond to outbreak emergencies and to develop optimal vaccines, diagnostic tests, and other critical materials. Consideration should also be given to reinforcing that any ABS portion of the agreement not deter innovation or act as a disincentive for industry participation.

4: The Global Health Threats Board or similar governance structure created by the G7/G20 PPR agenda, should negotiate to extend the mandates of CEPI, BARDA, the HERA Incubator, and equivalents elsewhere as appropriate, to support government-industry partnerships for R&D for influenza and other respiratory viruses with pandemic potential. These voluntary partnerships should focus on optimizing each industry partner's platform, using the following structure:

- **(a).** The G7 and G20 member nations (e.g., through the Global Health Threats Board) should name a global coordination body to specifically coordinate global and regional government-industry partnerships for influenza vaccines. CEPI is the existing multilateral global coordination vehicle for R&D, has access principles built in, and is a possible organization to assume this role.
- **(b).** Countries that fund vaccine R&D should ensure that R&D for pandemic influenza is part of their funding portfolio and strive to identify investment synergies to maximize returns on investments. Regional organizations should support the mobilization of government-industry partnerships, such as the Africa Centres for Disease Control, Association of Southeast Asian Nations, Gulf Cooperation Council, and Europe 2020's Innovation Union (funded by HORIZON 2020) and its successor.
- **(c).** Government-industry partnerships should have affiliated teams to identify promising technologies, optimize them for the field (e.g., identify adjuvants that enhance vaccine products on a small scale, to provide directionality in what to do during a surge), and consider investments required to reach efficiency yields. These partnerships should support Phase I-III clinical trials, as recommended by the United Kingdom/G7 PPP, as well as early dosing trials. They should also build-in workforce development training for areas of expertise required to be 'at the table' for technology transfer of these products.
- **(d).** Government-industry partnerships should share workforce development requirements with CEPI, the WHO, and other relevant multilateral partners, to help countries identify and fill gaps in ministries of health, labor, and economics expertise before a pandemic.

5: The Global Health Threats Board or similar governance structure created by the G7/G20 PPR agenda, working with other relevant organizations, should initiate a dedicated "moon-shot" program to incentivize development, licensure, and eventual procurement of a universal influenza vaccine candidate as a matter of priority. This program's structure and funding should include: (1) a "push" element for universal influenza vaccine R&D, which could be led by a variety of entities, including CEPI with input from its Scientific Advisory Committee, BARDA, the HERA Incubator, the WHO, the United States CDC, or other agencies that operate beyond the vaccine exploratory science phase and have a stake in market shaping, and (2) a complementary pull element (an AMC) to ensure procurement of resultant universal influenza vaccines, with technical leadership from Gavi and UNICEF (as a procurement agency for Gavi). This influenza moon-shot should be coupled with a parallel effort for coronaviruses or other respiratory viruses with pandemic potential that produce variants of concern. Financing for the push and pull elements for both virus families should do the following:

- **(a).** Receive funding from multilateral actors, development banks, philanthropies (e.g., Wellcome Trust and Bill and Melinda Gates Foundation), and regional governance structures, including but not limited to: the Organisation for Economic Co-Operation and Development (OECD), G20, World Bank/International Monetary Fund (IMF), regional development banks, the World Trade Organization (WTO), European Union (EU), and African Union (AU). This funding should be separately and individually supported by trade and global financing institutions of the United States, China, and the EU, such as the European Investment Bank (EIB) and Asian Infrastructure Investment Bank (AIIB).
- **(b).** Include participation from middle-income countries. The price for participation for these countries should be value-based and tiered; it should be determined by a value assessment (Health Technology Assessment) as part of the AMC. A financial intermediary such as a multilateral development bank should underwrite middle-income countries' own value-based AMCs, so countries do not need to put scarce resources aside until an effective product is approved.
- **(c).** Include country-specific tiered prices for guaranteed volumes of vaccines to multiple developers that meet the minimum efficacy threshold, to provide an incentive to retain multiple potential innovators. This would hedge risk against late failure of one or more early candidates and protect against the possibility of safety risks after widespread deployments that require restricted use or result in the first entrant's withdrawal from the market.
- **(d).** Include a requirement for successful vaccine innovator(s) to license their vaccines to other suppliers or manufacturers at low or zero cost, as a condition of accessing this guaranteed market. This will help facilitate widespread scale-up across all countries.
- **(e).** Be carefully costed over the next 1-2 years, to determine the scale of funding for this moon-shot that could reasonably derisk investments in influenza vaccine technologies.

6: The Global Health Threats Board or similar governance structure created by the G7/G20 PPR agenda should initiate a long-term (10-20+ years) multilateral partnership to track emerging technologies that may be targets for technology transfer for vaccines for influenza; promote industry partnerships with geographically distributed hubs; and provide technical training. To do so, it should do the following:

- **(a).** Identify or create an international entity to assume responsibility for catalyzing voluntary technology transfer initiatives for platform technologies, including influenza vaccines. The structure's governance should build on both the WHO and COVAX's work on the COVID-19 mRNA hub, expanding it to include a diverse portfolio of technologies capable of providing protection against diverse threats with pandemic potential, and the COVAX Vaccine Manufacturing Taskforce, expanding it to work with vaccine manufacturing bodies to identify supply chain inputs and needs across a variety of vaccine candidates.
- **(b).** Ensure that this entity promotes the development of platforms suited to the production of vaccines for other pathogens of national or regional importance in addition to seasonal influenza— or products such as therapeutics- including tracking technologies coming onto the market and building platforms for voluntary industry collaboration.
- **(c).** Develop or assist with the development of plans for geographically distributed hub training requirements, such as vaccine regulatory needs and vaccine product sourcing.
- **(d).** Encourage countries considering warming their manufacturing capacity for influenza vaccines and vaccines for other pathogens with pandemic potential to consider whether their focus should instead be on building new production capacity of key manufacturing inputs for vaccine manufacturing.
- **(e)**. Be given dedicated funding to support these activities from the World Bank and regional development banks, in conjunction with the International Finance Corporation (IFC).

7: UNICEF, Gavi, and relevant national and regional organizations (including governments) should be given funding explicitly allocated for introducing and deploying next-generation seasonal influenza vaccines to underpin scaled-up manufacturing capacity. WHO regional offices should urgently work with countries to do more extensive assessments of their readiness to reach appropriate populations, including adults and high-risk groups, to enable work plans by 2023, which include the following:

- **(a).** An analysis of what infrastructure (e.g., data and digitization of immunization records) built for COVID can be adapted, strengthened, and sustained for at least one additional adult and one adolescent vaccine.
- **(b).** Advising member states on best practices used in countries that had high immunization rates during COVID-19.
- **(c).** Assisting member states to look at their data and logistics systems for monitoring coverage and for tracking safety (pharmacovigilance) and on the options for adopting no-fault compensation as part of patient safety mechanisms.