Public Health Lessons for Non-Vaccine Influenza Interventions

Looking Past COVID-19

Alexander Capron, Patricia García, and Ellen Schenk, *Editors*

Committee on Public Health Interventions and Countermeasures for Advancing Pandemic and Seasonal Influenza Preparedness and Response

Board on Global Health

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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **SUSAN CURRY,** The

University of Iowa, and **SANDRO GALEA,** Boston University. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

National Academy of Medicine

Advancing Pandemic and Seasonal Influenza Vaccine Preparedness and Response Series

This study, Public Health Lessons for Non-Vaccine Influenza Interventions: Looking Past COVID-19, provides recommendations on how public health interventions and countermeasures can be used to mitigate the spread and effects of influenza both before and after vaccines are available. It is one of four studies conducted under the Advancing Pandemic and Seasonal Influenza Vaccine Preparedness and Response Initiative, which explores how the scientific and technological breakthroughs throughout the COVID-19 pandemic could inform and advance future pandemic and seasonal influenza vaccine preparedness and response efforts.

The three companion studies to this study examine how the lessons learned from COVID-19 around vaccine research and development, vaccine distribution and supply chain, and global coordination, partnerships, and financing could be best utilized to improve the development and distribution of future pandemic and seasonal influenza vaccines. Together, the four consensus studies present a path toward better preparedness in addressing pandemic and seasonal influenza.

Launched by the National Academy of Medicine with support from the Office of Global Affairs, U.S. Department of Health and Human Services, the Advancing Pandemic and Seasonal Influenza Vaccine Preparedness and Response Initiative acknowledges that influenza is here to stay. The unprecedented scope of this initiative allowed for international experts to look at this issue from multiple angles and provide recommendations that set out a pathway to more effective influenza vaccines worldwide. Driven by international cooperation, this independent initiative provides a platform to highlight why we need to act as a global community to better prepare for pandemic and seasonal influenza.

Acknowledgments

This study, very broad in scope yet on an extremely intense timeline, would not have been possible without the contributions and support from many. The committee would like to thank the speakers at the full committee meetings, whose names and affiliations are found in Appendix B. Many thanks are also extended to the Office of Global Affairs within the U.S. Department of Health and Human Services for sponsoring this effort, the international committee, coordinated by the National Academy of Medicine, for its thoughtfulness in developing the study's Statement of Task, and Victor Dzau for his enthusiasm and support.

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Preface

The first signal that a single nation, or the entire world, is about to experience a major problem—in the economy, the environment, public health, or any sphere that can touch the lives of countless people—is commonly termed a "wake-up call." Yet, the alarm sounded in this metaphor is unfortunately not one that brings a fire brigade to extinguish the flames but rather one that alerts us to the arrival of a peril that we knew—or could have anticipated—was coming but chose to disregard. In recent decades, as one novel infectious disease after another—H1N1 avian influenza, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome, and Ebola virus disease—emerged as a grave threat to human health, any public awakening to the weaknesses in national and global public health systems was only partial and seems to have soon subsided once the immediate threat had passed. Simply put, when those wake-up calls came, we rolled over and went back to sleep.

At the end of December 2019, a cluster of cases of atypical pneumonia was reported in Wuhan, China. The people affected were believed to have patronized a seafood market where wild animals were sold for human consumption. Chinese scientists rapidly sequenced the RNA of the novel coronavirus responsible for these cases—later named SARS-CoV-2—and submitted results to the U.S. National Center for Biotechnology Information on January 5, 2020. While that information was not immediately noticed, virologists around the world took note when the sequence data were published online on January 11. Two days later, Thai officials reported the first patient outside of China with coronavirus disease 2019 (COVID-19), a visitor from Wuhan who had not been to the seafood market, and the following

week, the national government acknowledged human-to-human transmission in China. At the end of January, the World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern, by which time, all nations might have been expected to have begun taking steps to contain the virus. But repeatedly, around the world, complete, transparent data were not communicated in a timely manner. Even as the warning signs became unmistakable, some governments censored doctors and journalists who drew attention to the disease, while leaders in other countries denied or downplayed the risk to their populations, even objecting to testing because it could reveal infections among asymptomatic people and thus make the situation seem more dire. Yet, had basic public health measures been implemented more quickly, modeling shows that some of the 216 million cases of COVID-19—and more than 4.5 million deaths—that have occurred globally as of this writing would have been avoided.

Numerous observers have found further wake-up calls in the COVID-19 pandemic itself: for example, leading medical journals have told their readers that it has revealed everything from the special vulnerability of elderly patients with cardiovascular disease and the stark health inequities that exist based on wealth and race (as seen in the unequal distribution of death and serious illness from the virus) to the fragility of the global economy and from the need for better global disease surveillance systems to the effectiveness of global collaboration in tackling pandemics.

The question facing us now is whether we have truly heeded these calls and, like an errant schoolboy, "learnt our lesson"? That too, draws on a familiar metaphor for what a reasonable person would expect to occur as the world takes stock of the social, economic, and personal devastation wrought by this pandemic. But how confident can we be that the core public health "lessons" of COVID-19—to say nothing of the broader message about the everyday effects of health inequities within and between nations—will result in adequate plans being created and implemented globally before the next pandemic strikes? And, in drawing lessons, we can learn not only to avoid governmental mismanagement and denial, which created public distrust and dissension and exacerbated the harms created by the pandemic, but also to replicate positive actions—such as the international cooperation among laboratory scientists, the ingenuity of researchers in creating—or repurposing—international clinical trial platforms to speed up the discovery of effective therapies, the selfless dedication of doctors, nurses, and other frontline health care workers, and the candor and clarity of some national officials in responding to the pandemic and thus promoting solidarity and cooperation among their citizens.

Trusting that this time the alarm has really woken countries up and that the lessons from COVID-19 will be taken to heart, the Office of Global Affairs in the U.S. Department of Health and Human Services asked the

National Academies of Sciences, Engineering, and Medicine to convene four ad hoc committees to step back and see what knowledge can be gained from the response of various actors, from the local to the global, to the present pandemic. We were asked to provide guidance on how to improve national and global preparations for and response to seasonal influenza and, more important, to the next influenza pandemic, which public health experts describe in terms of "when," not "if."

Our particular committee was charged with examining a wide variety of issues, as detailed in the Statement of Task that appears in Chapter 1. This assignment led us to explore topics ranging from zoonotic and medical surveillance along the frontier where novel viruses typically enter human society to the methods of testing for, and responding to, their occurrence in the community; from the efficacy of the nonpharmaceutical interventions used against SARS-CoV-2 that might also be relevant for influenza to the means of, and barriers to, implementing these measures effectively; and from the care of COVID-19 patients, especially when health care systems, in high- as well as low-income nations, are overwhelmed by sudden surges in hospitalizations, to the ways that therapy and innovation can be aligned through innovative trial designs when a new respiratory disease arises for which no biologic or pharmaceutical cures are known.

Because COVID-19 is a problem for all of humankind, and under the premise that "No one is safe until everyone is safe," the Office of Global Affairs requested that we produce advice that would be useful for all nations and the international organizations and other bodies that assist them in seeking to contain the spread, and mitigate the consequences, of novel—and potentially pandemic—strains of respiratory diseases. From the committee's first meeting at the beginning of March 2021, it was apparent how very fortunate we were to have five members from outside the United States and another three who are foreign scientists working in the United States, which provided us with detailed knowledge of country- and region-specific capabilities and weaknesses in responding to public health emergencies. Given the breadth of topics in our mandate, we are also grateful for the wide range of disciplines represented—not only medicine, virology, clinical research, epidemiology, and public health but also engineering, law, ethics, and communication science. Furthermore, the five members who have held high positions in international and national health agencies, including as minister of health, brought to our deliberations their firsthand experience with the real-world challenges of preparing for and responding to outbreaks of infectious diseases. We also thank the experts and members of the public who contributed their knowledge and experience during our public meetings, our consultant Marc Lipsitch, and our project staff at the National Academies who, as always, deserve credit for what is good in this report but no blame for any shortcomings.

As we finish our work, it is daunting to realize that increasing numbers of scholars are concurrently publishing new findings about various aspects of the ongoing pandemic, which necessarily lends a provisional cast to our conclusions. Still, we have been reassured when other bodies engaged in dissecting the pandemic arrive at points that align with our findings, conclusions, and recommendations. For example, regarding surveillance, the Independent Panel on Pandemic Preparedness and Response, appointed by WHO, recognized in May the need for both devising better means to regulate the forces that are causing zoonoses to become an increasing health threat to domestic animals and the humans who tend them and implementing the One Health strategy to ensure rapid identification of "spillovers" from wild animals that pose pandemic risks. Likewise, others have identified the need to revise the International Health Regulations to strengthen WHO's ability to investigate outbreaks and share its findings and to recognize that, under certain conditions, controlling cross-border movement of people and goods can be effective in preventing the initial spread of a novel pathogen. As many groups have also acknowledged, the barriers that caused many people to suffer adverse health outcomes when they were unable to fully comply with recommended COVID-19 countermeasures did not arise solely from the lack of necessary supplies in many communities at the outset of the pandemic. Rather, whether the countermeasure depended on having effective face masks, living in housing that made physical distancing possible, or receiving income support that would permit quarantining or isolating, noncompliance resulted from the systemic factors in society that already prevent certain people from achieving "the highest attainable standard of health," which is their right as human beings.

It is our hope that beyond specific lessons of the sort described in the pages that follow, the COVID-19 pandemic and the horrific human toll, economic devastation, and troubles for all sectors of society that it has wrought have finally convinced governments, civil society, the business community, and the general public the truth of the adage that, when it comes to public health, an ounce of prevention is unquestionably worth far more than a pound of cure. It would be folly indeed if we wait for another "wake-up call" before using what this pandemic has taught us to ready our societies for the next one.

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Committee on Public Health Interventions and Countermeasures for Advancing Pandemic and Seasonal Influenza Preparedness and Response

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BOXES

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Acronyms and Abbreviations

ACTT-1	Adaptive COVID-19 Treatment Trial 1
AI	artificial intelligence
AMR	antimicrobial resistance
API	active pharmaceutical ingredients
ARI	acute respiratory infection
CFR	case fatality ratio
CI	confidence interval
COVID-19	coronavirus disease 2019
DNA	deoxyribonucleic acid
ECDC	European Centre for Disease Prevention and Control
EISN	European Influenza Surveillance Network
EMS	emergency medical services
EUA	Emergency Use Authorization
FDA	U.S. Food and Drug Administration
GHSI	Global Health Security Index
GIS	Global Influenza Strategy
GISRS	Global Influenza Surveillance and Response System
GPHIN	Global Public Health Intelligence Network

HEPA	high-efficiency particulate air
HIV	human immunodeficiency virus
HVAC	heating, ventilation, and air conditioning
ICU	intensive care unit
IHR	International Health Regulations
ILI	influenza-like illness
JEE	Joint External Evaluations
LMIC	low- and middle-income country
mAb	monoclonal antibody
MERS	Middle Eastern respiratory syndrome
MERS-CoV	Middle Eastern respiratory syndrome-related coronavirus
NAM	National Academy of Medicine
NIH	National Institutes of Health
NPI	nonpharmaceutical intervention
OECD	Organisation for Economic Co-operation and Development
PAHO	Pan American Health Organization
PANDORA-ID-NET	Pan-African Network for Rapid Research, Response, Relief and Preparedness for Infectious Disease Epidemics
PCR	polymerase chain reaction
PPE	personal protective equipment
qPCR	quantitative polymerase chain reaction
R_0	basic reproduction number
R&D	research and development
RCT	randomized controlled trial
RECOVERY	Randomized Evaluation of COVID-19 Recovery Therapy
REMAP-CAP	Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia
RNA	ribonucleic acid

Rt	effective reproduction number
RT-PCR	reverse transcription polymerase chain reaction
SARInet	Severe Acute Respiratory Infections Network
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SSA	sub-Saharan Africa
UKAID	UK Aid Direct
U.S. CDC	U.S. Centers for Disease Control and Prevention
USDA	U.S. Department of Agriculture
UV	ultraviolet
UVGI	ultraviolet germicidal irradiation
WHO	World Health Organization

Summary

The coronavirus disease 2019 (COVID-19) pandemic has challenged the world's preparedness for a respiratory virus event, with more than 180 million people infected and an estimated 3.916 million deaths by the end of June 2021 (WHO, 2021). While the world has been combating COVID-19, seasonal and pandemic influenza remain imminent global health threats. Seasonal influenza causes 250,000 deaths on average worldwide each year (Madhav et al., 2017), and influenza remains the circulating pathogen most likely to cause a pandemic. In a given year, the probability of pandemic influenza causing 6 million pneumonia and influenza deaths globally is 1 percent (Madhav et al., 2017).

Coronaviruses and influenza viruses have a number of similarities and differences that merit consideration when drawing lessons from the COVID-19 pandemic for influenza events: for example, influenza has a shorter incubation time, and children are usually greater drivers of community transmission (Brownstein et al., 2005).

Both before and after a vaccine is available, public health control measures—such as face masks and improved physical distancing—can combat emerging and ongoing influenza outbreaks by mitigating transmission. Non-vaccine measures during the COVID-19 pandemic contributed to shortening the 2019–2020 influenza season by 4–7 weeks in the Northern hemisphere (Stojanovic et al., 2021) and dramatically reducing influenza activity globally (Karlsson et al., 2021), although increased coverage of influenza vaccines and virus–virus interactions may also have contributed. Efforts to combat the effects of seasonal and pandemic influenza can be

strengthened by drawing on lessons from the COVID-19 pandemic on the need for effective research on, and implementation and sustained use of, non-vaccine interventions.

With these issues in mind, an ad hoc committee of experts under the auspices of the National Academies of Sciences, Engineering, and Medicine examined the COVID-19 experience for lessons on the efficacy and implementation of non-vaccine public health interventions and countermeasures to strengthen preparedness for, and response to, future influenza events (see Box 1-1 in Chapter 1). After its deliberations, the committee concluded that a comprehensive, coordinated approach to preparedness and response is required.

KEY FINDINGS AND CONCLUSIONS

Event Preparedness

- Preparedness should include investments to expand holistic strategies, such as the One Health approach, to build surveillance capacity, improve the accuracy of data collection through defining critical data elements, and develop and maintain data integration platforms to ensure the timely detection of zoonotic pathogen strains with pandemic potential and large antigenic drifts and shifts.
- Preparedness efforts should consider the capacities to research, produce, and stockpile therapeutic drugs for respiratory viruses, including any supplies needed for their delivery.
- Methods for data collection, monitoring, and adjustments for response plans should be included in preparedness efforts.
- Preparedness efforts should include research into non-therapeutic mitigation strategies and supplies.

Event Response

- When sociocultural, economic, and other contextual factors are taken into account, non-vaccine control measures offer an effective means of responding to future seasonal and pandemic influenza events. To minimize the harm to lives and livelihoods, these measures should be deployed simultaneously in a layered fashion, accompanied by rigorous data collection, monitoring, and adjustments to the combination of measures in light of the evidence accumulated.
- For non-vaccine control measures to be effective, people must be able and willing to use them, which means that necessary resources

and support are distributed equitably and the value that they provide to individuals and the public is communicated clearly.
- A critical part of responding to a pandemic is conducting adaptive platform trials and rigorous research of therapeutics.

Surveillance and Data Collection

Despite the need for proactive efforts to detect a pathogen with pandemic potential, such as coronavirus, before its widespread transmission, current surveillance tools and strategies are primarily designed to monitor known pandemics and ongoing seasonal influenza. A holistic One Health approach is required to target surveillance more effectively across the domains of human, animal, and environmental health. Knowledge gleaned from this type of collaborative, transdisciplinary approach could strengthen the abilities to detect, test, study, and monitor existing and novel zoonotic pathogen strains for antigenic drifts, shifts, and pandemic potential. Success with this strategy as a part of harmonized and coordinated pandemic preparation and response will depend on countries and intergovernmental bodies adopting a shared commitment to bolstering national and international surveillance capacities.

Contemporary public health surveillance, including testing and contact tracing, uses cutting-edge technologies, such as leveraging mobility data, conducting sewage surveillance, analyzing crowdsourced data streams, and building collaborative tools, including data-sharing platforms and entities. Survey design is key for producing accurate data upon which policy decisions are made. It is important to avert biases in designing surveillance, collecting data, and analyzing and interpreting the data in order to provide accurate information to decision makers.

Recommendation 2-1: The World Health Organization, the World Bank, and regional public health organizations should work collaboratively with countries (particularly 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 to develop and support interagency One Health platforms.

Recommendation 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, notify authorities to take these biases into account, and seek support for improving surveillance methods to better achieve representativeness and sufficient geographical coverage.

Recommendation 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.

Recommendation 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.

EFFECTIVENESS OF NON-VACCINE CONTROL MEASURES

According to available evidence, when correctly fitted to the wearer, face coverings such as respirators, surgical/procedural masks, and multilayer woven cloth face masks are the most effective non-vaccine control measure in reducing the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); face shields alone are not effective. Additionally, physical distancing measures have some evidence for effectiveness, but the current recommendations of 1–2 meters do not account for physiology and physics of exhalation flows, their interaction with airflows, and viral particle distribution in droplets and the exhalation cloud. These considerations highlight the importance of ventilation for reducing virus transmission in closed indoor public places where people do not typically wear masks (e.g., restaurants) and the need to integrate the various non-vaccine intervention measures into a more holistic framework, including

both individual and community actions. In addition to ventilation, evidence suggests that air filtration may mitigate transmission by reducing virus concentrations in the air in closed indoor places. However, little evidence exists for the effectiveness of barriers, which may even be harmful, if they impede air circulation.

The COVID-19 experience has shown that government-mandated controls aimed at keeping people apart, such as curfews, lockdowns, and restrictions on gatherings, are effective in reducing viral transmission. Applying this lesson to influenza, it is likely that school closures would be relatively more effective, because children shed influenza viruses for longer and at higher levels than adults. Nonetheless, COVID-19 control measures to limit or prevent contact outside of the home had other social, economic, political, and health effects that have to be balanced when developing policies to mitigate an influenza outbreak.

Although mass- and risk-based testing and contact tracing were used in many countries during the COVID-19 pandemic, influenza viruses have shorter incubation periods than SARS-CoV-2, meaning these measures are likely to be less effective for influenza.

Measures such as travel restrictions and border closures used by some countries—particularly island nations—were sometimes effective in reducing the spread of COVID-19. However, the World Health Organization (WHO) does not recommend these, because the International Health Regulations (IHR), a legally binding framework, do not recommend strict border closures that may impact international travel and trade.

To further explore the validity of these conclusions, a research framework using diverse evidence from multiple disciplines, such as physical sciences and engineering, is needed to assess individual and combined nonvaccine control measures for respiratory viruses. Ecological and observational studies are required to collect evidence on interventions considered to be too broad or unethical to assess via a randomized controlled trial (RCT).

Recommendation 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.

Recommendation 3-2: Global, state, and local public health agencies and other entities should mandate wearing face masks that comply with the World Health Organization's guidance, when justified by the incidence and severity of influenza.

Recommendation 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.

Recommendation 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.

Recommendation 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.

Implementation of Non-Vaccine Control Measures

A number of social, cultural, structural, and other contextual factors have influenced the public's reception to and uptake of non-vaccine control measures during the COVID-19 pandemic. Such public responses can be profoundly shaped by a range of beliefs and norms that vary across communities around the world; policies and intervention plans need to take these into account when mitigation strategies for respiratory viruses are designed and implemented.

The effectiveness and uptake of non-vaccine control measures is ultimately contingent upon cooperation that is spearheaded by strong leadership and coordinated governance and communication. As the COVID-19 pandemic illustrates, swift, proactive government action and effective harmonization within and across sectors—supported by leaders who model the recommended behavior—ultimately influenced public receptivity to and use of such measures. While social, cultural, and other contextual factors play pivotal roles, governments are the primary actors in determining how non-vaccine interventions are communicated and deployed.

The COVID-19 pandemic exacerbated the racial, socioeconomic, and other health inequities that affect many people's lives. These inequities often led to heightened risk of coronavirus exposure due to occupational or living conditions, as well as greater disease severity and mortality fueled by a higher prevalence of comorbidities. Hence, strategies for successful implementation of non-vaccine control interventions should take into account community-specific social and structural determinants of health, particularly by using data and frameworks to measure and ensure the equi-

table impact of such interventions, which may require providing resources adapted to overcome existing barriers and inequalities.

Recommendation 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.

Recommendation 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 communicating 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").**

Recommendation 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.

Recommendation 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.**

Therapeutics

As demonstrated by the COVID-19 response, pandemics spur the need to rapidly identify, manufacture, and distribute therapeutic drugs. It also showed the importance of having mechanisms in place that are ready to conduct international collaborative trials of existing and novel therapies, singly and in combination, and of stockpiling any therapeutic agents known to be effective and the supplies that are essential for drug delivery and the full course of care. Guidance is also needed on how to distribute scarce and novel therapeutics equitably and clearly for patient care. Universal principles will need to guide this allocation in ways that build trust by preventing health systems' collapse and removing allocation decisions from frontline providers.

Adaptive platform trials conducted with shared global protocols allow for comparing interventions and adjusting participant enrollment as evidence on therapeutics evolve. During a pandemic, these platforms can be leveraged to test promising therapeutics when RCTs may not be feasible. To ensure progress in therapeutic research, global cooperation, coordination, and collaboration should be sustained between governments, private companies, and global organizations, perhaps through models such as WHO's Solidarity trials and data-sharing efforts to obtain evidence on therapeutic safety and efficacy.

Recommendation 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.**

Recommendation 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.**

Recommendation 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.

Recommendation 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.

This study advocates for policy makers and other stakeholders to give concerted attention to non-vaccine control measures for seasonal and pandemic respiratory viruses. Although many prominent research agendas and initiatives for respiratory viruses focus on vaccines, non-vaccine interventions are the first line of defense for mitigating transmission. This is obviously true before a vaccine exists. However, as an outbreak or pandemic evolves and vaccines are developed, such interventions continue to be simple, cost-effective countermeasures, which makes them an essential part of any effort to end an outbreak, since vaccines are neither completely effective nor immediately available to everyone at risk. Furthermore, when infections do occur, therapeutics are the last line of defense to avert the effects. Therefore, research to develop and test non-vaccine control measures should be a priority, particularly in low- and middle-income country settings, to enable governments to best leverage such measures during respiratory virus events. The next novel influenza or other respiratory pathogen posing a severe threat to human health is a matter of when and where, not if. Strategic prioritization of non-vaccine control measures at the global, regional, and local levels is needed now.

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1

Introduction

Influenza poses a serious threat to health around the world. Seasonal influenza results in about 1 billion cases annually, leading to 3–5 million patients with severe illnesses (WHO, 2019), of whom an estimated 294,000–518,000 die (Paget et al., 2019). The effects of an influenza pandemic would be even greater. In 2019, when releasing its Global Influenza Strategy for 2019–2030, the World Health Organization (WHO) acknowledged that it is only a question of when, not whether, the next influenza pandemic will happen and that many experts believed a severe outbreak could be one of the most devastating global health events ever, with potentially far-reaching health, social, and economic consequences (WHO, 2019). As the world struggles to recover from the death and devastation caused since early 2020 by another respiratory virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), could nations, international organizations, and the private sector draw any useful lessons from the coronavirus disease 2019 (COVID-19) pandemic as they prepare for an influenza outbreak?

To strengthen countries' preparedness for and response to seasonal and pandemic influenza, WHO's Global Influenza Strategy (GIS) provides a comprehensive framework, from surveillance to prevention and control interventions. Building on the success of the Global Influenza Surveillance and Response System and the Pandemic Influenza Preparedness Framework, the GIS focuses on developing programs at the country level and investing in health systems strengthening as a means of enhancing pandemic preparedness. Yet, the response to COVID-19 has revealed gaps and opportunities for improvement in global efforts to prepare for a major outbreak of respiratory viral disease. As of May 18, 2021, 162,184,263 people worldwide had been

infected (WHO, 2021); 3,364,446 deaths have been recorded, but worldwide cases remain underreported by more than half, and based on the weekly excess death rate during the pandemic, the actual toll is estimated at 6.9 million deaths (IHME, 2021). While the response to COVID-19 continues, the global threat of emerging seasonal and pandemic influenza remains, underscoring the need to harness experiences garnered from COVID-19 and other previous influenza responses to update and advance preparedness efforts.

Coronaviruses and influenza viruses have a number of similarities and differences that factor into applying lessons from the COVID-19 pandemic to influenza events. Both infect the respiratory tract via surface proteins, result in similar symptoms, and have animal reservoirs (Abdelrahman et al., 2020). Influenza has a shorter incubation time, 1–4 days compared to 2–14 days. The variability in incubation time for SARS-CoV-2 has implications for public health strategies, such as the utility of testing and contact tracing. Both viruses are highly contagious and can remain on surfaces for more than 24 hours (ASM, 2020), yet research has shown that children shed influenza viruses longer and at higher levels (Heald-Sargent et al., 2020; Ng et al., 2016). However, as the Delta variant of SARS-CoV-2 became the dominant global strain in summer 2021, children were more likely to be affected. As new variants emerge, it will be important to maintain awareness of the similarities to and differences from influenza and other SARS-CoV-2 strains.

Non-vaccine control measures can be a vital defense during a respiratory virus pandemic—both before and after vaccines are available—and thus warrant special attention amidst efforts to strengthen preparedness. Once a new virus is identified, it can take at least 4–6 months to develop vaccines and many months more for clinical trials, regulatory processes, and eventual emergency use authorization or approval. Furthermore, producing and deploying vaccines can be constrained by variable and low to nonexistent supplies and limited manufacturing capacity across the world. On the other hand, non-vaccine control measures can be affordable, effective, and broadly implementable (PAHO, 2009). For example, a modeling study estimated that nearly 130,000 additional lives could have been saved from COVID-19 in the United States between September 2020 and February 2021 if 95 percent of the population wore face masks in public (Reiner et al., 2021). However, such measures globally have historically not been fully used during a pandemic: early case detection, contact tracing and isolation, quarantine, physical distancing, ventilation, hand hygiene, mask wearing, and travel restrictions are not always applied comprehensively or consistently enough to curb transmission, morbidity, and mortality (PAHO, 2009). Some interventions may be used too early or too late, delaying their impact and causing undue economic and social hardship, limiting the public health benefits, and reducing long-term public compliance and trust (Independent Panel for Pandemic Preparedness and Response, 2021).

Information has evolved during the COVID-19 pandemic on guidance for non-vaccine measures that can have implications for influenza control interventions. In fact, COVID-19 mitigation measures contributed to a marked decrease in influenza, with virtually no influenza season in fall 2020 and a 2019–2020 influenza season that was shortened by an estimated 4–7 weeks in the Northern hemisphere (Stojanovic et al., 2021). In the Southern hemisphere, influenza was almost absent as well in winter 2020 (Sullivan et al., 2020). While guidance on the use of non-vaccine public health measures has been widely published in many high-income countries, less attention has been directed toward understanding how to optimize such measures on a global scale in a way that accounts for unique social and political factors across the diverse contexts of low-, middle-, and high-income countries. Sustaining such levels of decreased influenza transmission may require ongoing compliance with COVID-19-era non-vaccine interventions to minimize the reservoir of viruses in populations where vaccination percentages remain below herd immunity rates (Solomon et al., 2020). Overall, the response to COVID-19—including both best practices and systematic gaps identified—offers an opportunity to reevaluate priorities for influenza and strengthen preparedness for seasonal and pandemic influenza.

PROJECT ORIGIN AND STATEMENT OF TASK

At the request of the U.S. Department of Health and Human Services' Office of Global Affairs, the National Academies of Sciences, Engineering, and Medicine (the National Academies) created an initiative to advance pandemic and seasonal influenza vaccine preparedness and response by harnessing lessons from the efforts mitigating the COVID-19 pandemic. The National Academy of Medicine (NAM) convened a committee of domestic and international experts from across sectors (e.g., government, academia, industry, civil society, international public health organizations) and a variety of disciplines to provide an iterative process informed by experts for analyzing the impact that lessons learned during COVID-19, in particular with regard to the technologies, policies, and processes developed worldwide, could have on pandemic and seasonal influenza global preparedness and response. This committee developed the Statements of Task for four concurrent National Academies ad hoc committees.[1]

The Committee on Public Health Interventions and Countermeasures for Advancing Pandemic and Seasonal Influenza Preparedness and Re-

[1] Information about the initiative and the other three studies can be found at https://www.nationalacademies.org/our-work/advancing-pandemic-and-seasonal-influenza-vaccine-preparedness-and-response-harnessing-lessons-from-the-efforts-to-mitigate-the-covid-19-pandemic (accessed November 18, 2021).

sponse (the committee) was convened to analyze the use of non-vaccine control measures for respiratory viruses, primarily during COVID-19. It was charged with recommending actions specifically related to non-vaccine public health interventions that could strengthen preparedness for seasonal and pandemic influenza. Box 1-1 provides the full charge to the committee, which included 12 members with academic and professional expertise in disease surveillance, therapeutics, non-vaccine public health and engineering interventions, communications, behavioral and social health, ethical aspects of public health, and other disciplines. Appendix A provides the biographies of the committee members and the staff who put together the report.

BOX 1-1
Statement of Task

An ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine will examine the preparedness for and response to prior influenza pandemics and COVID-19 for lessons learned on the efficacy and implementation of non-vaccine public health interventions and countermeasures for implications for future influenza events. The study will focus on the tasks below to produce a report with recommendations for best practices for implementing public health measures, diagnostics, and therapeutics to mitigate the spread and effects of influenza both before and after vaccines are available.

1. Analyze the evidence of effectiveness of key non-vaccine measures (e.g., masks, indoor air quality, and ventilation) developed across disciplines, and novel or existing diagnostic tools that can be adapted and optimized to mitigate respiratory infections such as, but not limited to, seasonal and pandemic influenza. The evidence should be underpinned by the biology and epidemiology of specific disease outbreaks;
2. Explore the social and political context (e.g., societal inequities, stakeholder trust, and communication) underlying the effective implementation and optimization of priority public health measures and diagnostics to identify best practices for future pandemic influenza preparedness and response;
3. Review promising COVID-19 therapeutic approaches (e.g., antivirals, monoclonal antibodies, and host-directed responses) with demonstrated effectiveness in particular to highlight critical opportunities to use therapeutics for seasonal and pandemic influenza;
4. Highlight innovations around the world during COVID-19, as well as other seasonal and pandemic influenza events, particularly related to surveillance and rapid, transparent data sharing, that can lead to best

BOX 1-1 Continued

practice recommendations for notification, contact tracing, and testing efforts, including the use of digital technology and data science; and

5. Analyze prominent research agendas, existing research initiatives, and knowledge gaps identified from the response to COVID-19 and other outbreaks to outline priority actions for future research efforts related to seasonal and pandemic influenza. These priority areas may include evidence and knowledge generation for strengthening surveillance systems, the effectiveness and implementation of priority health measures, or diagnostic tools for influenza viruses, such as sequencing and testing.

COMMITTEE APPROACH AND STUDY SCOPE

This study responds to a need to strengthen efforts to mitigate influenza, which was identified in the 2019–2030 WHO Global Influenza Strategy (WHO, 2019), the 2020–2030 U.S. National Influenza Vaccine Modernization Strategy (HHS, 2020), and other documents. In developing the report, the committee deliberated for approximately 4 months. Between March and early June 2021, the full committee met virtually three times, each time for 9 hours over multiple days. The first two full meetings included open sessions during which the committee heard from the sponsor and speakers to fulfill key information-gathering needs. Appendix B includes all of the public meeting agendas with speaker names and topics, and Appendix C provides further details of the study approach.

This study aims to provide a brief, high-level introduction to the many broad, complicated topics encompassed in the Statement of Task. Analysis of the study topics drew primarily from the rich and extensive expertise of the committee members. Staff initiated the analyses with literature searches (the terms of which are presented in Appendix C) to outline the key issues related to the Statement of Task, focusing on systematic reviews and highly cited articles. Identification of priorities, including further sources and subtopics to explore, was based on expert guidance from the committee. This study offers evidence from select sources; it is not intended to provide a comprehensive or systematic review of all available evidence or the many subtopics related to the points within the Statement of Task. The committee chose to prioritize the topics presented in the following chapters and predominantly focused on drawing lessons for future pandemics rather than seasonal events. The sources stemmed primarily from literature focused on the response to the COVID-19 pandemic that was published through early June 2021 in the form of select journal articles, case studies, examples, and news media articles. In addition to publications featuring original research

and evidence, the committee considered sources that examined the process of implementing non-vaccine control measures during COVID-19, explored critical opportunities to use therapeutics to mitigate disease progression, and reviewed surveillance-related successes, challenges, and innovations. With regard to the fourth point in the Statement of Task, upon initial analysis, most of the lessons learned and recommendations for best practice seemed to stem from inadequacies with core surveillance capacities. Given the challenge with defining what would qualify as an innovative approach and the dearth of evidence on the effectiveness of innovations, the committee focused on ways to strengthen core surveillance systems with consideration of innovative approaches, while not allowing such attention to detract from its primary focus. The committee considered both the level and strength of the evidence to provide specific recommendations on measures that could be used most effectively on a global scale and those with potential effectiveness but a lack of sufficient research or data. With the broad nature of the Statement of Task, the committee could not identify specific organizations that would have complete responsibility over particular areas of the study, so some of the recommendations likewise are broad. Given the study timeline and scope of the committee's charge, the committee largely chose not to focus on the following issues: workforce training and capacity; interventions for health care workers (as opposed to the general population); and vaccine hesitancy.

The committee drew on the best science and expert testimony available in summer 2021. In the context of the ongoing global pandemic, which continues to evolve rapidly, we recognize that new data are continuing to emerge, especially related to new variants of the virus. Thus, this report reflects the state of the science during the period when the committee was working, and some points may become outdated as new studies are completed and new data become available.

ORGANIZATION OF THE REPORT

This report follows the Statement of Task, with the next four chapters corresponding to its first four points (see Figure 1-1). Chapter 2 explores the topics of the fourth point: surveillance-related lessons learned during COVID-19. Chapter 3 covers the evidence of effectiveness of non-vaccine control measures, defined in this chapter as their value in reducing virus transmission, which is followed in Chapter 4 by considering contextual factors that can affect implementation and population optimization of such measures. Chapter 5 explores opportunities to use therapeutic approaches. Each of these chapters also examines relevant research gaps and priorities, which is the fifth point in the Statement of Task. The study findings are discussed in the background sections of Chapters 2–5, while overarching

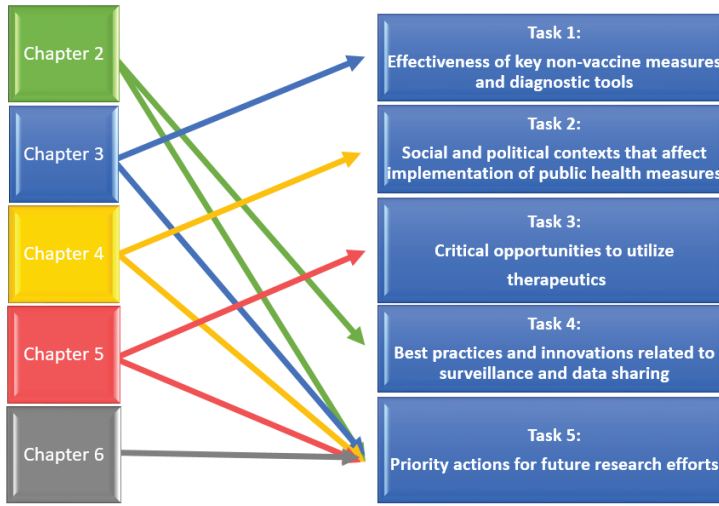

FIGURE 1-1 Crosswalk between the report chapters and study Statement of Task.

conclusions and recommendations from the findings appear at the end of each chapter. Closing thoughts are presented in Chapter 6, which summarizes the main conclusions and discusses the way forward and opportunities for research.

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2

Surveillance

The coronavirus disease 2019 (COVID-19) pandemic has exposed gaps in the capacity of worldwide national health systems and global-level systems to detect emerging and reemerging pathogens—including possible zoonotic threats, new strains of influenza with pandemic potential, and antigenic drifts in known viruses—before an outbreak occurs and a response is required. To close these gaps, countries need to collaborate to create early warning systems that are supported by political commitment, stable governance, and sustainable financing. Effective outbreak surveillance is urgently needed, since epidemics and pandemics are likely to become more frequent due to factors such as the expansion of urbanization, the growth and intensification of livestock production, more extensive and rapid global travel and trade connections, the effects of climate change, and pervasive socioeconomic inequities. Fortunately, the COVID-19 pandemic has also revealed the benefits of leveraging political will and financial resources to realize this early warning surveillance network for future emergent pathogens (Carroll et al., 2021).

PREPAREDNESS FOR SURVEILLANCE DURING THE COVID-19 PANDEMIC

Various indicators and indexes have been developed in recent years to evaluate countries' level of preparedness, identify gaps and weaknesses, and support strengthening their capabilities to prevent, detect, and respond to outbreaks, epidemics, and pandemics of infectious diseases. For example, the Global Health Security Index (GHSI) draws on open-source informa-

tion to assess and benchmark health security and related capacities in 195 countries (JHU, 2019). Similarly, WHO's Joint External Evaluations (JEEs) have been used for evaluating a country's ability to prevent, detect, and respond to infectious diseases and outbreaks. Countries ranked higher in terms of preparedness according to GHSI, JEEs, and other indicators would be expected to respond more effectively to an actual pandemic event; however, that was not the case for COVID-19. An evaluation of the predictive value of GHSI and JEEs found that countries' health preparedness scores were not correlated with detection response times or mortality outcomes (Haider et al., 2020). Furthermore, responsibilities for countries to act on their GHSI scores and improve preparedness are not necessarily delineated. A rank-based analysis of Organisation for Economic Co-operation and Development (OECD) countries' ability to respond to COVID-19—based on total cases, deaths, tests, and recovery rates—found that their pre-pandemic GHSI preparedness scores did not predict their actual response; the scores tended to overestimate some countries' preparedness and underestimate others (Abbey et al., 2020). A study evaluating the correlation between countries' GHSI scores and measures of COVID-19 burden found no association between GHSI and rate of testing and, unexpectedly, a positive association between GHSI and cases and deaths (Aitken et al., 2020). An analysis of imported COVID-19 cases reported across 49 countries in sub-Saharan Africa (SSA) as of April 2020 found that the countries with high (1) GHSI scores, (2) likelihood of severe cases, and (3) government effectiveness rankings were not necessarily reporting a higher incidence of cases or more information per case. Such gaps in information could indicate undetected transmission and illustrate the difficulty of detecting and responding to asymptomatic cases (Skrip et al., 2021). More broadly, these disparities between predicted preparedness and actual response to a pandemic highlight shortcomings in the way preparedness has been assessed. Furthermore, given the increasing degree of global interconnectedness, "identifying and controlling spread of newly arising infectious agents is only as effective as the practices within the poorest performing countries" (Aitken et al., 2020, p. 354).

ROLE OF SURVEILLANCE IN MITIGATING RESPIRATORY VIRUS OUTBREAKS

Surveillance has different functional roles in the context of a respiratory virus outbreak: (1) detecting potential new threats outside of a jurisdiction that could potentially be imported and spread locally, including epizootic, zoonotic, and epidemic threats; (2) detecting the importation and community transmission of an identified outbreak threat in animals and humans; and (3) assessing the extent and severity of an outbreak using forecasts and models. The first two roles focus on detecting a threat quickly and accurately, while

also minimizing false-positive test results; in some scenarios, these efforts may warrant oversampling high-risk locations (e.g., ports of entry). In contrast, activities to fulfill the third role—quantifying the spread—are situated in the realm of systems-based processing of large volumes of human samples, collected in a representative way, to understand the current number of cases and how that epidemiological landscape is changing.

Syndromic Surveillance for Infectious Diseases

Over the past two decades, syndromic surveillance has been used as a strategy for detecting and monitoring public health events based on individual- or population-level indicators in advance of confirmed diagnoses of an emerging infectious disease. For example, data on symptoms or clinical diagnoses such as influenza-like illness (ILI) or severe acute respiratory illness could serve as early indicators that an unusual respiratory pathogen is circulating (van den Wijngaard et al., 2008). These indicators and data on pneumonia of unknown origin were used retrospectively by Chinese authorities and WHO to assess evidence for early cases of COVID-19 (WHO, 2021b). Syndromic surveillance is theorized as advantageous for early detection of infectious disease outbreaks, given the time lags between initial symptoms and a clinically or laboratory-confirmed diagnosis (Chu et al., 2012). A retrospective study found that syndromic data from health registries—including on work absenteeism, general practice consultations, prescription medications dispensed, diagnostic test requests, hospital diagnoses, and deaths—correspond to patterns in respiratory pathogen activity and thus can be used for surveillance (van den Wijngaard et al., 2008). Beyond the early detection value, syndromic surveillance data can also inform public health actions, contribute to improved situational awareness, and bolster the credibility of public communications. Clinical laboratory testing that includes signs and symptoms, with data aggregated in the cloud, can also serve as a type of surveillance when syndromic trends are reported, including negative test results (Meyers et al., 2018). If enough negative results are reported in a certain region linked to people with severe symptoms, it could be a signal of a new pathogen and trigger the need for additional testing. This was used during H1N1 in 2009 and again in Wuhan when the outbreak first began; syndromic panels were negative for pneumonia, leading to identifying a novel virus. Incorporating health systems, including academic health institutions and the data they collect, can strengthen global public health infrastructure, even for pathogens not often targeted by surveillance. This is an opportunity to add scale and capacity to public health.

Box 2-1 describes some of the major influenza surveillance collaboratives that serve to do so. Syndromic surveillance conducted alone, such as with ILI systems, or in combination with viral testing can be and has been used to

track activity in real time during a pandemic (Brammer et al., 2011; Lipsitch et al., 2009; Shaman et al., 2011). However, a qualitative study of syndromic surveillance during the 2009 H1N1 pandemic in Ontario, Canada, found that it had only a limited impact on decision making about public health response activities, which were largely informed by logistics (e.g., vaccine availability) and traditional forms of surveillance using laboratory data (Chu et al., 2012).

BOX 2-1
Summary of Major Surveillance Collaborations

Influenza Surveillance System: The U.S. Centers for Disease Control and Prevention (U.S. CDC) collects, compiles, and analyzes influenza data through a voluntary collaboration between the organization and its state, local, and territorial health departments, laboratories, statistics offices, and care organizations. The system (1) conducts virologic surveillance, where respiratory illnesses are sampled for influenza virus types, subtypes, lineages, and the age groups affected, characterizing the genetic and antigenic composition of the virus, and conducts surveillance for novel influenza A viruses. The surveillance system also reports (2) outpatient influenza-like illness, (3) the geographic spread of influenza, (4) influenza-associated hospitalizations, and (5) mortality surveillance associated with influenza, COVID-19, or pneumonia (CDC, 2020).

Severe Acute Respiratory Infections Network (SARInet): In the Americas, a diverse range of professionals across countries, organizations, and health-related organizations participate in the SARInet. These efforts are supported by the World Health Organization, the Pan American Health Organization, and U.S. CDC and are intended to complement and, where needed, compensate for ministry of health capacity in the region. They share, learn, and collaborate to enhance the epidemiological understanding of influenza and other respiratory viruses (SARInet, 2021).

European Influenza Surveillance Network (EISN): In Europe, the EISN uses reports from sentinel general practitioners, pediatricians, and other specialty physicians. Each EISN member reports new cases of either influenza-like illness or acute respiratory infections, but some members report both (ECDC, 2021).

Global Influenza Surveillance and Response System (GISRS): Since 1952, the GISRS has protected people from seasonal, pandemic, and zoonotic influenza through collaboration and virus and data sharing. The system serves as a global platform for monitoring influenza epidemiology, an alert system for novel influenza viruses and other respiratory pathogens of concern, and a mechanism for influenza surveillance, preparedness, and response. The GISRS consists of collaborating centers across 123 countries, primarily National Influenza Centers and WHO Collaborating Centers for (1) influenza research and reference material; (2) influenza epidemiology, surveillance, and control; and (3) ecological studies on influenza in animals. There are also regulatory and reference influenza laboratories (WHO, 2021c).

ONE HEALTH APPROACH

The existing wealth of knowledge and evidence-based strategies for mitigating epidemic and pandemic threats remains largely untapped and underused. For instance, "One Health" is a collaborative, multilevel, transdisciplinary approach that aims to achieve optimal health outcomes between people, plants, and animals in their shared environment (CDC, n.d.). It is increasingly recognized by governments, scientists, the private sector, nongovernmental organizations, academic partners, and others as an effective way to combat health threats that affect people, animals, plants, and the shared environment. One Health approaches are particularly relevant to emerging infectious diseases, of which greater than 60 percent are zoonotic, and to diseases that have a strong link to environmental conditions (e.g., water- and vector-borne diseases). Many of these diseases spill over to humans through a complex and multi-step process (see Figure 2-1). This type of surveillance effort is especially critical in low- and middle-income countries (LMICs) and places that have an extensive human–animal interface.

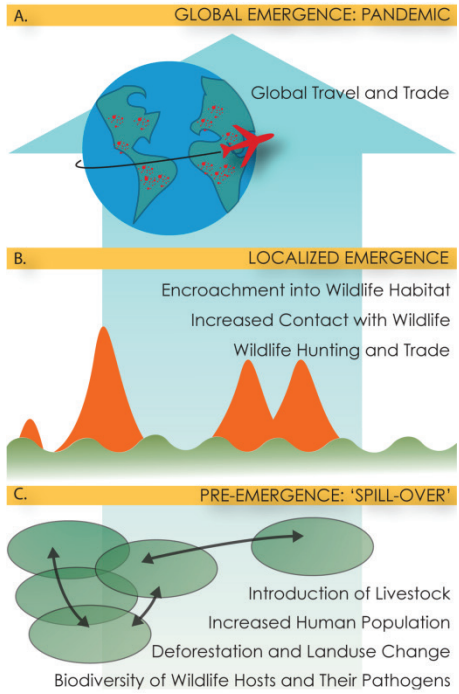

FIGURE 2-1 Figurative description of the multi-scale, multi-step process of pandemic emergence.
SOURCE: Bogich et al., 2012.

In one review of nearly 400 public health events of international concern, a breakdown or absence of public health infrastructure was identified as the driving factor for just under 40 percent of outbreaks. Though many outbreaks do not result in global pandemics, pandemic prevention at the local level should include stronger public health infrastructure, expanded surveillance, and incorporation of development agencies into strategies that target where populations intersect with the environment (Bogich et al., 2012).

Evidence for One Health Approaches and the Need for This Type of Surveillance

Earlier studies have recommended active surveillance through One Health approaches to mitigate infectious disease threats as discussed during an Institute of Medicine workshop on emerging viral threats (IOM, 2015). Some of these recommendations have been implemented, but not to the extent that outbreaks such as COVID-19 could have been prevented, despite the warning signs and knowledge about how to use One Health approaches to intervene. For example, forming One Health outbreak investigation teams that involve veterinarians, medics, social scientists, wildlife biologists, and ecologists could enable more rapid investigation of the zoonotic origins of emerging diseases, something that was not a focus of early COVID-19 investigations. Done well, One Health approaches can lead to higher returns on investment through joint human–animal disease surveillance and control measures (Kelly et al., 2020). Ongoing exercises working across sectors also help to facilitate collaboration and connect stakeholders that do not typically interact, improving future communications.

Interagency One Health platforms have been launched in LMICs specifically to link operations of ministries of health, agriculture, and the environment and wildlife, while also maximizing surveillance for influenza and other emerging zoonoses. Because South Asia has been identified as a "hot spot" for emerging zoonotic disease, it has focused on strengthening One Health efforts since the early 2000s, along with many bilateral and multilateral partners. For example, Bangladesh has seven One Health research programs, offers three One Health postgraduate degrees at various universities, and has field epidemiology training programs for public health and laboratory personnel through the U.S. CDC (McKenzie et al., 2016). It also developed a Strategic Framework for One Health Approach to Infectious Diseases in 2012, which was endorsed by the Ministry of Health with widespread support (IEDCR, 2012).

Through multi-sector collaboration in Kenya, the government developed an institutional framework to highlight the importance of several types of diseases that informs capacity building programs, surveillance, and workforce development, among other areas. It has noted improved

outbreak response and newly generated data that informed disease control programs and increased preparedness (Munyua et al., 2019). The ability to more easily share disease outbreak information across sectors and rapid response at the county level has been credited with reducing spillover to humans in an anthrax outbreak in 2016. More recently, the country has deployed a syndromic surveillance system in domestic and wild animals, using a mobile phone application for reporting and analysis, with hopes to improve real-time surveillance within the animal health sector. Stakeholders involved in this effort believe that "the adoption of the One Health program and approach in Kenya has led to rapid detection and control of zoonotic disease outbreaks at their source and thereby enhanced global health security" (Munyua et al., 2019).

Lessons from COVID-19

The emergence of SARS-CoV-2 has reinforced the rising risk of pathogens that are capable of jumping species to humans. Despite a wealth of evidence on different wildlife species and the types of viruses they carry, the connection between that knowledge and what measures are needed to reduce the risk of spillover is more tenuous. After SARS in 2003, substantial research in China and Southeast Asia demonstrated a wide diversity of related viruses in wildlife (bats in particular) and that some of these were able to infect human cells in vitro and cause SARS-like disease in mice with human ACE2 receptors (Ge et al., 2013; Latinne et al., 2020; Menachery et al., 2015). Farming wildlife known to act as SARS intermediate hosts continued to expand, with around 14 million people employed in the industry in China alone in 2016 (UNDP China, 2017). Furthermore, published evidence revealed that people in rural China were infected by bat SARS-related coronaviruses even without direct involvement in hunting or consuming wildlife (Wang et al., 2018). These studies were widely cited in the literature and cited by WHO in the rationale to include SARS-related coronaviruses as "priority pathogens" for vaccine and therapeutic development through the R&D Blueprint effort. A small number of researchers globally were funded to develop therapeutics (e.g., remdesivir). However, efforts to close down wildlife farms, markets, and trade networks or remove known coronavirus hosts were not widely undertaken until after the COVID-19 outbreak began. Likewise, widespread funding of vaccine or therapeutic development through the U.S. National Institutes of Health, Coalition for Epidemic Preparedness Innovation, or R&D Blueprint did not occur prior to the outbreak. This example demonstrates that the knowledge generated through One Health approaches and research can provide important insight, but until the political motivation exists to act on the findings and provide funding, the problems will remain unsolved and likely surface again.

After SARS in 2003, China instituted a program of syndromic surveillance that did form part of the early warning system for clusters of pneumonia cases that were later diagnosed as COVID-19. The improved surveillance and laboratory capacity in 2020 was able to recognize the novel outbreak within just a few weeks of syndromic surveillance clusters (Chan et al., 2020).

Challenges to Achieving an Effective One Health Approach

Many experts recognize the barriers to widespread, practical implementation of a One Health approach across contexts. Ultimately, inadequate funding mechanisms, lack of incentives for collaboration, and competing interests across different government ministries pose major barriers to implementing One Health principles. Although some countries have created dedicated One Health task forces and crosscutting mechanisms linking ministries of health, environment, agriculture, and wildlife, they have been ineffective at scale and at the global level. Additionally, a review of One Health literature in 2017 found few efforts to systematize metrics and truly evaluate outcomes versus merely modeling projections (Baum et al., 2017). Of more than 1,800 papers, only 7 reported quantitative outcomes, and even these did not use a shared methodology. Without a standardized framework to capture metrics for these types of approaches, it will be difficult to encourage more widespread adoption of One Health. Another concern highlighted by multiple sources is sustainability of programming. A collection of three case studies in Africa concluded that broad institutional changes and sufficient funding are needed for One Health to become a more common approach to health policy at the national levels, and each country will need its own individualized plan based on its needs and capacities (Okello, 2014).

A key challenge that has been highlighted by the COVID-19 pandemic is a lack of connection between the evidence of a potential pandemic threat and forming policies to deal with it. Evidence that viruses related to SARS-CoV were present in wildlife and livestock in China was funded by research agencies and published in scientific papers but not brought into a formal risk assessment framework. Similarly, wildlife farming and trade were considered the likely causes of the emergence of SARS, but policies to conduct coronavirus surveillance as a routine for wildlife hunters, farmers, or traders, or the animals they sold were not formalized into the public health system. Collecting influenza samples and identifying strains from wild birds and farmed animals is routine in some countries but could be expanded in many others. However, challenges include difficulties in assessing the pandemic potential of novel strains, as sequencing and pursuing all of those identified would quickly exhaust available resources and workforce.

BOX 2-2
Examples of Research Topics Regarding One Health

- Developing a risk assessment framework for novel viruses or strains discovered in wildlife, farmed, or traded animals.
- Identifying key interfaces where spillover and then spread are most likely to occur, using data on wildlife species distribution, livestock, and human population surveys.
- Identifying animal species that are likely to be viral reservoirs to specifically target surveillance programs via phylogenetic and molecular virological approaches.
- Enhancing target surveillance and identifying pathways for viral spillover through behavioral risk surveys in people.

To be optimally effective, One Health collaborative approaches should be truly international—not just interagency—and leverage the power of established regional and global health organizations. Expanded collaboration among national development agencies, such as the United States Agency for International Development, as well as multilateral organizations (e.g., WHO, Food and Agriculture Organization of the United Nations, World Organisation for Animal Health, United Nations Environment Programme, and World Bank and regional equivalents), should also be encouraged in the One Health sphere. More areas for additional research to inform this approach can be found in Box 2-2.

RELEVANT FINDINGS AND CASE STUDIES FROM THE COVID-19 PANDEMIC

This section provides an overview of COVID-19 findings and case studies that demonstrate successes, highlight innovations, and illustrate challenges related to surveillance for respiratory pathogens.

Core Public Health Functions for Surveillance

Core public health functions for surveillance include identification and notification, sampling and genomics, and testing and contact tracing for event notification and control. Strengthening these capacities will be critical to more effectively prepare for and respond to future epidemic and pandemic events.

Tracking Outbreak Progress

Pandemic statistics—particularly the proportion of the population infected—are believed to be generally and substantially underestimated. Contributing factors related to the limitations of classical surveillance approaches include insufficient diagnostic capacity, failure to detect asymptomatic cases rapidly enough, and political shortcomings of following through on outbreak predictions. The COVID-19 pandemic has included cases in which traditional surveillance methods have underestimated the actual prevalence. For example, polymerase chain reaction (PCR) testing for detecting infections is hampered by limited testing capacity, high rates of false-negative results, and the test's inability to detect asymptomatic and subclinical infections (Silverman et al., 2020). An analysis of the use of influenza surveillance networks to estimate U.S.-state-specific SARS-CoV-2 prevalence has suggested that during the early phases of the pandemic, greater than 80 percent of infections were undetected (Silverman et al., 2020). Hospital-based surveillance has limited utility in accurately estimating the number of cases, because many people who test positive are not hospitalized (Alwan, 2020), or there are delays in obtaining timely clinical data (Garg et al., 2020). However, in some localities, it may have contributed to mitigating the initial spread. For instance, in Singapore, such a surveillance and containment strategy has been documented as contributing to improved case ascertainment and slowing transmission (Ng et al., 2020). Telehealth data could also contribute to surveillance systems in a pandemic context, particularly if many patients are not hospitalized and virtual visits are encouraged as an infection control measure (Koonin et al., 2020).

Sampling and Genotyping

Laboratory science is a cornerstone of successfully controlling an epidemic or pandemic. Core components of an effective laboratory response include (1) building testing capacity early, (2) preparing the workforce for a dynamic response, (3) strengthening information management systems, and (4) creating laboratory partnerships that can be leveraged during an event (McLaughlin et al., 2021).

During the COVID-19 pandemic, genotyping and genomic surveillance have been valuable tools for detecting new variants and understanding their potential effect on infectivity and health outcomes (CDC, 2021a). Understanding the genomic diversity of an infectious pathogen can inform more effective strategies to contain its spread during the initial stages of an outbreak. For example, in the highly interconnected region spanning Maryland and Washington, DC, in the United States, more than 2,500 cases of COVID-19 were reported within 3 weeks of the first detected case in

March 2020. Genomic sequencing analysis of 114 complete viral genomes revealed a broad diversity that included all the lineages that were known to be circulating globally at the time, signifying that multiple introductions of the virus into the region were likely. Moreover, a combined analysis of those genomes with clinical metadata determined that clinically severe cases had originated from all the major lineage strains (Thielen et al., 2021). Genomic sequencing is also valuable for seasonal and pandemic influenza (CDC, 2021b).

However, this level of genomic surveillance is not universally conducted, making it difficult to obtain a global view of dominant strains in different areas. While SARS-CoV-2 led to an acceleration of efforts, without supplemental epidemiology and surveillance data, the genomic sequencing is not sufficient to show which strains are more transmissible or more lethal (Morgan et al., 2021). Some countries cannot afford the technology, nor do they have sufficient workforce; others, such as the United States, have not invested in the infrastructure because it was not seen as widely important until recently and fragmented data systems make it difficult to coordinate and share across institutions. For example, the United States was ranked thirty-third in the world during this pandemic, with less than 2 percent of cases sequenced. The COVID-19 Genomics UK Consortium (COG-UK), set up in April 2020, is an example of what a well-functioning system would look like and that others could model.[1] After just 1 year, COG-UK had sequenced more than 450,000 genomes, contributing to the United Kingdom's rank of fifth in the world, sequencing more than 8 percent of its cases (Maxmen, 2021). COG-UK has a long-term goal of developing a sustainable sequencing network across the United Kingdom. The consortium includes partners from the National Health Service, public health agencies, academic partners, lighthouse labs, and the Wellcome Sanger Institute.

Individual- and Population-Level Testing

At the individual level, COVID-19 testing strategies include quantitative PCR (qPCR), loop-mediated isothermal amplification, and antigen testing performed at the point of care, central laboratories, or through rapid testing modalities. At the population level, testing strategies range from pooled testing to screening to surveillance of wastewater and surfaces. However, the optimal strategy for a given setting is context specific and not necessarily universal—different approaches are warranted to serve various purposes (Mina and Andersen, 2021). Diagnostic testing aims to identify people with SARS-CoV-2 infection, for both clinical management and isolation, contact

[1] For more on the COVID-19 Genomics UK Consortium, see https://www.cogconsortium.uk/cog-uk/about-us (accessed August 28, 2021).

tracing, and contact testing. Although the relatively lengthy time to results from laboratory-based PCR testing reduces its utility in preventing transmission, rapid point-of-care tests can enable more widespread testing coverage. The goals of surveillance testing are to conduct representative sampling to estimate prevalence and inform response activities at the population level. Antibody testing can be used to understand the breadth of historical exposure, while ongoing community transmission can be monitored through PCR testing of wastewater or pooled testing in low-prevalence settings, for example. Screening, which includes entry screening and public health mass screening efforts, can be used to detect people who are a- or pauci-symptomatic but may be infectious. Rapid antigen tests can offer reduced costs and short turnaround times, particularly in places where reverse transcription (RT)-PCR capacity is limited. For COVID-19 screening, rapid antigen tests perform best in presymptomatic and early symptomatic cases with high viral load up to 5 days from symptom onset. Their shorter turnaround times for results and lower costs can facilitate community testing regardless of symptoms in homes, care settings, and workplaces that may face risks of high levels of community transmission (ECDC, 2021).

The COVID-19 pandemic has demonstrated the extent to which virological, genotyping, and population-wide serological surveillance can be limited by testing capacity (de Lusignan et al., 2020). Efforts to bolster preparedness for future events are ongoing in countries in Africa and other regions to strengthen testing and other capacities to enhance public health surveillance systems, such as by integrating pathogen genomics (Inzaule et al., 2021). Evidence suggests that programs with expanded testing capacity during COVID-19 effectively curtailed transmission. In late 2020, Slovakia implemented a strategy of population-wide rapid antigen testing and additional restrictions on social contact in 45 counties; modeling suggests that these measures—as well as isolation of household contacts—were associated with a 58 percent reduction prevalence within 1 week of implementation (Pavelka et al., 2021).

Contact Tracing

Contact tracing can contribute to not only curbing transmission of an infectious disease threat—via identifying and isolating exposed contacts—but also reducing case fatality rates through early detection and referral to care (Yalaman et al., 2021). Drawing on evidence from 138 countries, an analysis of different contact tracing strategies and COVID-19 case fatality rates found that comprehensive contact tracing—along with appropriate case isolation—was associated with significantly reduced case fatality rates, even after controlling for public health and social measures and the number of tests performed (Yalaman et al., 2021).

Contact tracing was also demonstrated to be successful during the West African Ebola outbreak in 2014–2015, most notably in Nigeria. Thanks to establishing a field epidemiology and laboratory training program in 2008, hundreds of Nigerian health workers were trained in contact tracing, outbreak investigations, and report development. The Nigerian program was the first to apply the concept of One Health in full, because it included epidemiology, laboratory, and veterinary tracks (Oleribe et al., 2015). The teams had worked together through Lassa Fever and polio outbreaks and were designed to be interdisciplinary, so they were poised to respond rapidly to the Ebola outbreak and can be a model for future outbreaks.

During the COVID-19 pandemic, few countries had a sufficient number of trained personnel to conduct contact tracing, particularly during the early stages. Even settings where contact tracing was initially effective faced difficulties in sustaining those efforts as the pandemic unfolded. In Germany, initial contact tracing was largely successful until capacity became overwhelmed as infections peaked (Loh, 2020; Reintjes, 2020). In summer 2020, as case numbers began to decline, many countries devoted more resources to increasing testing capacity than to building contact tracing capacity or ensuring that people who became infected could appropriately isolate (Loh, 2020).

A review of COVID-19 contact tracing efforts in Nigeria, Rwanda, South Africa, and Uganda provided several best practices, challenges, and lessons informing future implementation of these efforts. The common challenges identified across all five countries include internal stigma, community resistance, and apathy driven by mistrust and perceived and internal stigma. Another critical common challenge was misinformation and an overwhelming load of contact tracing and case detection workload for health care workers. For example, the number of contact tracers per 100,000 population ranged from a low of 3 in some areas to a high of 186. Other challenges identified included fears around contact tracers' risk of COVID-19 infection, limited testing and health care capacity, mistrust of political entities, and poor adherence to quarantine and isolation guidelines and rules. Lessons learned from these nations broadly included the effectiveness of decentralizing and building capacity for communication, contact tracing, testing, and their associated human resources at the local and community levels. Additionally, the authors found that interoperable data and technology should complement traditional contact tracing efforts to improve decision making. Partnerships, meaningful community engagement, and coherent political leadership were identified as mechanisms to build trust, combat misinformation, and scale interventions (Nachega et al., 2021).

The general effectiveness of contact tracing varies across settings and contexts. An analysis of COVID-19 countermeasures in Yamagata Pre-

fecture, Japan, found that retrospective contact tracing efforts to identify epidemiological links were likely effective in halting the first wave (January–May 2020) (Seto et al., 2021). According to a mathematical modeling study, a combination of highly effective contact tracing and isolation was sufficient to bring a new outbreak under control within 3 months, but the likelihood of control declines if fewer cases are detected through contact tracing (Hellewell et al., 2020). A simulation study found that a testing capacity of 0.7–9.1 tests per 1,000 population would be needed to contain the spread of SARS-CoV-2, depending on public health and social measures in place, and that the number of new daily infections did not always decline—it could exponentially increase if contact tracing and testing efficacy fell lower than 60 percent (Fiore et al., 2021).

Variations in the effectiveness of contact tracing can be attributable to the number of observed asymptomatic infections, transmission efficiency, population distribution and size, and the size of the secondary infection cluster. This suggests that when developing testing and contact tracing strategies, policy makers should consider population-level density, geographical distribution, and travel behavior (Fiore et al., 2021). Moreover, most strategies mainly employ a "forward-tracing" protocol to notify people that they were exposed to a known case. However, a bidirectional tracing approach also includes reverse tracing, which seeks to identify the parent case who infected the known case, as well as other cases related to that parent case. A modeling study has suggested that bidirectional tracing is a more robust approach to outbreak control for COVID-19, yielding a reduction in the effective reproduction number (Rt) more than twofold greater than forward tracing alone (Bradshaw et al., 2021).

CHALLENGES IN PUBLIC HEALTH SURVEILLANCE HIGHLIGHTED DURING THE COVID-19 PANDEMIC

COVID-19 has revealed multiple limitations of current public health surveillance systems and tools, which were primarily designed for ongoing surveillance of known pandemics and seasonal influenza rather than for early detection and mitigation of respiratory pathogens with pandemic potential. These existing systems are also unable to accommodate the sustained surge capacity necessitated by a large-scale global pandemic event. Specific challenges that undermine the ability to conduct syndromic surveillance and interpret surveillance data include (1) the effect of media reporting early on; (2) changes in health-seeking behavior driven by pandemic-control measures, such as physical distancing; and (3) changes in systems for clinical coding and patient management (Elliot et al., 2020). Strengthening central systems for data use, collection, and sharing would allow for more effective quantification of the spread of infection and optimal

parameterizing for forecasts and models. Furthermore, in addition to the strategies described below, core surveillance capacities can be strengthened through reiterative testing via simulations and other exercises (Reddin et al., 2021).

Ascertainment Bias

Ascertainment bias is a consequence of biased sampling that has likely undermined efforts to estimate the burden, infectiousness, and fatality of SARS-CoV-2 since the outset of the pandemic (see Box 2-3). Such biases can misinform the public about the severity of a disease and the utility of public health interventions in general or for particular subgroups (Peixoto et al., 2020). For example, using case fatality rates based on hospital fatality rates, which include only a small subset of individuals with the disease, has led to misunderstanding that alarmed the public and inaccurate comparisons of disease severity between COVID-19 and Ebola (Winters et al., 2020).

Inaccurate epidemiological estimates based on nonrepresentative or inaccurate data have also led to ill-advised policy decisions and ineffective responses. For months at the outset of the pandemic, the U.S. government was unable to estimate how many people were sick with COVID-19, were hospitalized, or had died (Meyer and Madrigal, 2021). Levels of com-

BOX 2-3
Ascertainment Bias and COVID-19 Case Fatality Ratios

A case fatality ratio (CFR) is the proportion of deaths from a disease with the number of individuals diagnosed with the disease. Calculating accurate CFRs is critical in supporting the COVID-19 pandemic response. CFRs can help quantify the risk for different demographics and enable practical and accurate resource planning and allocation (Angelopolous et al., 2020).

Also called "sampling bias," underascertainment of mild cases can incorrectly increase CFRs. For example, the cumulative number of confirmed cases in New York City, with a population of 8.55 million (NYC Planning, 2021), reached 72,181 on April 6, 2020 (NBC New York, 2020). However, a state seropositivity study, measuring the amount of virus in the blood, estimated that around 21 percent of city residents had contracted COVID-19 (Goodman and Rothfeld, 2020).

Collecting randomized data by testing close contacts of positive individuals regardless of symptomatic presentation could mitigate sampling bias by limiting the covariance, or the relationship, between diagnosis and death (Angelopoulos et al., 2020), which could help better communicate the risk of death from COVID-19 and how the fatality risk varies across different demographic groups within a population (Kobayashi et al., 2020).

munity and background transmission were underestimated in many U.S. localities, which could have been rectified by routine standardized testing, which can mitigate sampling bias (Angelopoulos et al., 2021). Instead, the White House Coronavirus Task Force relied on forecasts from the Institute for Health Metrics and Evaluation during the initial days of the pandemic (IHME, 2020). This model made a number of inaccurate assumptions: that the epidemic curve would follow the outbreaks in China and Italy (Holmdahl and Buckee, 2020), that physical distancing measures would remain effective, and that social distancing was being implemented the same everywhere (Jewell et al., 2020). Its initial projection—a death toll of only around 60,000 U.S. individuals (which was actually surpassed by May 2020)—influenced state and federal officials to pivot to reopening the economy instead of prolonging physical distancing and other public health measures (Cancryn, 2020). Other countries, such as Brazil, reduced testing, resulting in underreporting disease incidence (Fonseca, 2021). In contrast, China demonstrated the value of improved testing strategies. Early in the outbreak, diagnosis was based only on testing that had severe capacity constraints; when the case definition was expanded to include radiological criteria as an adjunct, it contributed to elucidating the true infection rates (Tsang et al., 2020). Additional research needs related to ascertainment biases can be found in Box 2-4.

Variability in Estimating Infectiousness and Fatality Rates

Wide variability has been observed between country- and state-level COVID-19 infectiousness and fatality rates. For instance, a Bayesian modeling study—which was designed to minimize ascertainment bias—analyzed confirmed data on COVID-19 cases, deaths, and recoveries from U.S. states

BOX 2-4
Examples of Research Topics Regarding Ascertainment Biases

- Studying the shape and size of the "clinical iceberg" in different contexts.
- Understanding sampling frames of reported statistics and how to harmonize data from different sources to derive robust incidence/prevalence estimates.
- Determining clinical severity estimates (e.g., case fatality risks) that have well-characterized denominators and monitoring their evolution by stage of epidemic and with different treatment interventions.
- Developing novel methods to take into account sampling biases, particularly in genomic surveillance where low- and middle-income countries receive poor coverage.

and countries in all world regions. By April 2020, estimates of infectivity ranged from 9–13 unreported cases for every confirmed case globally. At the outset of the pandemic, the estimated mean global reproduction number and total infection fatality rate were 3.3 (confidence interval [CI] 1.5, 8.3) and 0.17 percent (CI 0.05–0.9 percent), respectively. By mid-April, estimates for those values had evolved to 1.2 (CI 0.6, 2.5) and 0.8 (CI 0.2–4.0) percent. Moreover, the variability observed between the country- and state-level values implies substantial uncertainty about the ability to accurately assess an epidemic's current state or trajectory (Chow et al., 2020). In terms of the earliest fatality risk estimates, a crude case fatality rate of 3.67 percent was found among cases from mainland China (Verity et al., 2020) and a case fatality risk of 1.4 percent in Wuhan (Wu et al., 2020). In contrast, an early analysis in Italy found crude case fatality rates of 10.6 percent nationwide and 18.3 percent in Lombardy, much higher than the rates estimated based on data from outbreaks in China and aboard the Diamond Princess cruise ship (1 percent) (Vicentini et al., 2020).

Clinical Icebergs

COVID-19 exemplifies challenges caused by the "clinical iceberg" phenomenon: the relative proportions of clinically observed infections versus unobserved infections. Quantifying those proportions is critical to developing the parameters for models to elucidate population-level transmission dynamics and epidemic trajectories that are needed to inform public health policy (Wu et al., 2020). Most cases of respiratory pathogens in particular go undiagnosed and not notified, underscoring the need for surveillance and detection systems that "search for the unexpected" and unseen.

Underrepresentative Sampling Frames

A general limitation of survey-type seroprevalence studies is the underrepresentation of vulnerable populations at high risk of COVID-19 infection and/or mortality (e.g., residents of nursing homes, persons who are homeless, persons who are incarcerated, or persons living in large urban slums or refugee camps) due to challenges related to reaching and sampling those populations. Lack of representativeness in sampling frames undermines the ability to accurately estimate COVID-19 prevalence (Bendavid et al., 2021) and SARS-CoV-2 seroprevalence, as exemplified in a study that inferred the total number of people infected in all of Croatia from a serosurvey of just two factories (Ioannidis, 2021). However, some approaches have achieved a much greater degree of sampling representativeness, thus yielding more accurate estimates. Luxembourg implemented a mass screening program during the early summer 2020 wave of COVID-19 that aimed to capture

a representative sample of the entire population—including residents and cross-border workers—and found a significant attack rate among asymptomatic cases (Wilmes et al., 2021). Similarly, a representative, nationwide, population-based serological survey in Spain reported that at least one-third of people with COVID-19 were asymptomatic, underscoring the importance of early testing and detection (Pollán et al., 2020). Related, although it was against the convention early in the pandemic to only test individuals with a connection to China, the Seattle Flu Study was one of the first to find community transmission in the United States by testing study samples for SARS-CoV-2 (Chu et al., 2020). This further illustrates how diagnostic testing can be an effective response, that each community will have different levels of risk, and testing may be more useful in some circumstances more than others (Sharfstein et al., 2020). Further needs for research related to transmission are highlighted in Box 2-5.

Strengthening Reporting

Institutional hierarchies and bureaucracies can stifle reporting on the progress of an outbreak. For instance, officials may be hesitant to trigger investigations by reporting on diseases of concern due to fear of stigma or the economic implications, as observed with Ebola in central and West Africa. Other layers of bureaucracy in reporting can also delay a response. For instance, within the African integrated disease surveillance response system, health facilities report to district and national levels of health authorities on priority diseases of importance; these then report to global institutions, which can be slow to respond. Reporting could also be strengthened by involving the communities—training and providing tools to frontline public health workers and community workers in accurately detecting, reporting, and analyIng during routine public health surveillance for priority diseases; this can help to ensure timely, complete, and accurate data for decision making. Using a case study designed to train resident epidemiologists in

BOX 2-5
Examples of Research Topics Regarding Transmission

- Determining the mode of transmission of emerging new strains (e.g., airborne versus large droplets).
- Understanding temporal dynamics in viral shedding and transmissibility to determine relative contributions of presymptomatic versus asymptomatic versus pauci- or full symptomatic spread.

Liberia, it is possible for 1–2 instructors to train up to 20 students in collecting useful data, auditing data quality, and conducting Strengths, Weaknesses, Opportunities, Threats analyses (Frimpong et al., 2017). Incentives are another mechanism to strengthen reporting during outbreaks. Different incentives may be most effective at different levels, such as country-level incentives of funding and resources, increased prestige for effective systems, and international encouragement (IOM and NRC, 2009).

Zoonotic Surveillance

The interface between humans, domesticated animals, and wild animals is a major locus for the emergence of zoonotic diseases, which comprise the majority of emerging infectious disease threats reported worldwide. Coronaviruses and avian influenza viruses are among the foremost zoonotic threats to human health (Huong et al., 2020), with evidence suggesting that SARS-CoV-2 may be due to zoonotic transmission that may have originated in or been subsequently amplified at a live animal market in Wuhan (Tiwari et al., 2020; WHO, 2021b). The COVID-19 pandemic and other epidemics of zoonotic origin of recent decades have underscored the need for One Health approaches to strengthen zoonotic surveillance efforts, detect viral strains with larger antigenic drifts, and develop better strategies to understand the degree of potential threat posed by emerging strains.

Live Animal Markets

Live animal markets provide ideal conditions for zoonotic transmission through an intimate interface among animals and people, leading to amplification of pathogen load and the potential for recombination or selection pressure for evolution of virulence. These factors highlight the need for more effective surveillance strategies in these settings (Tiwari et al., 2020). Multiple zoonotic influenza viruses have been associated with human exposure to animals at these types of markets and further down wildlife and poultry supply chains. An evaluation of wildlife supply chains for human consumption in Vietnam (2013–2014) used PCR testing to detect coronavirus sequences, finding high proportions of positive samples in field rats (34.0 percent) to be consumed by humans and among bats in guano farms near human residences (74.8 percent) (Huong et al., 2020). The analysis also found a mix of different types of bat and avian coronaviruses in rodent feces, suggesting that the mixture and amplification of coronaviruses along the wildlife supply chain to retail and restaurant settings could increase the potential for zoonotic spillover to consumers.

During the epidemic of avian influenza A H7N9 (2013–2015), which causes human infections primarily via zoonotic transmission, closing live

poultry markets in mainland China temporarily halted outbreaks (Peiris et al., 2016). However, such measures are not feasible over the long term, due to the country's existing systems for live poultry production and marketing. In China and other countries in Asia, live poultry systems dominate poultry consumption. These systems, which are complex and do not tend to be intensively regulated, span a large network of farm production, transportation to wholesale markets, and retail distribution (Peiris et al., 2016). More sustainable and less disruptive approaches to reducing the risk of emergence and transmission of zoonotic influenza include instituting market "rest days," banning live poultry in markets overnight, and separating terrestrial poultry from live ducks and geese; such strategies have been progressively implemented in Hong Kong (Peiris et al., 2016). Alternative strategies for reducing the risk of zoonotic viruses, beyond simply banning all live animal markets, have concomitant environmental and social benefits, including encouraging smaller-scale meat production, improving market hygiene, implementing more stringent regulations at markets, and outlawing the trade of certain wildlife (Petrikova et al., 2020). Others have argued that banning wildlife trade would effectively bolster the black market, so tighter regulation would be more effective (Tiwari et al., 2020).

Coordination and Assessment

An analysis of WHO's JEE reports looked at trends in preparedness for high-consequence zoonotic infectious diseases among SSA countries (Elton et al., 2021). The veterinary workforce had the highest average score in all categories across all countries evaluated; response mechanisms had the lowest average score. Most countries provide public health training courses for veterinarians. The Southern African region had the highest mean score for all zoonotic disease categories. All five of the most frequently cited zoonoses on priority pathogen lists in SSA were neglected diseases: rabies, highly pathogenic avian influenza, anthrax, brucellosis, and bovine tuberculosis (TB). These findings suggest that SSA countries should leverage the convergence of public health, veterinary, and environmental government departments across African and global health organizations—such as the One Health consortia and the Pan-African network PANDORA-ID-Net—to implement a collaborative One Health approach to pandemic preparedness and response (Elton et al., 2021).

With increased genomic capacity for detection of novel viruses, a better strategy to assess risk of novel agents is needed. The recently published SpillOver is a comprehensive, publicly accessible risk assessment tool for systematically evaluating novel infectious viruses' potential for zoonotic spillover and spread. Although data gaps limit the ability of SpillOver to rank relative animal–human transmission risk, among other challenges,

the tool and its associated watch lists can support virus discovery efforts to detect new animal viruses, assess and communicate risk, and inform pandemic preparedness and response efforts (Grange et al., 2021). It also offers opportunities for global collaborative research to understand the biology of pathogens that may be emergent and screen therapeutic agents in advance. Ideally, this would be available as a global repository of information that can be accessed widely by researchers.

Data Collection, Use, and Sharing

Digitally enabled public health strategies augmented by data science can aid in population surveillance, case identification, contact tracing, and evaluation of interventions based on mobility data and public communications. Harnessing the power of digital technologies through a combination of mobile phones, large online datasets, interconnected devices, low-cost computing resources, machine learning, and natural language processing underpins these efforts. Efforts are now focusing on ways to effectively and ethically incorporate data from digital and Web-based sources into public health surveillance—for example, through hybrid approaches that integrate data from traditional sources with data collected from Internet search queries, posts on social media networks, and other forms of open-source and crowdsourced data (Aiello et al., 2020). Metadata and line lists can be one informative way of linking data streams (Xu et al., 2020). In a pandemic, social media can serve as a powerful mechanism for communicating and disseminating information. However, a scoping review found that social media data were not leveraged for real-time surveillance to detect or predict cases during the COVID-19 pandemic as they have been for other infectious diseases, such as malaria and influenza (Tsao et al., 2021).

Within nations, sharing surveillance data across communities can be vital for identifying an outbreak's impact (Liverani et al., 2018). However, two-way accountability is needed for entities with capacity to take immediate action on data and surveillance information that is shared by countries. Inefficiencies in collecting and sharing data among health agencies and across countries impeded the flow of information on critical treatment, patient, and event-level data during COVID-19 (Cossgriff et al., 2020). Another critical need is to standardize and harmonize data to enable data sharing (Fukushima et al., 2018). Additionally, practical issues, such as the location and method of long-term storage and maintenance, access control, and funding, are unresolved for epidemiologists and public health researchers (Pisani and AbouZahr 2010). Nevertheless, a model that has been used for event notification is Participatory One Health Digital Disease Detection; community members use smartphone and other web applications to report unusual disease events in humans and both wild and backyard animals;

these reports lead to a local response from health experts (Ending Pandemics, 2021). Another possible model to incentivize data reporting and sharing is the Global Initiative on Sharing Avian Influenza Data, which fosters collaboration by requiring data users to provide credit to submitters and also work to include them in joint viral data analyses (LoTempio et al., 2020).

Digital Contact Tracing Technologies

Functions of digital contact tracing technologies include outbreak response, proximity tracing, and symptom tracking (Anglemyer et al., 2020). During the COVID-19 pandemic, digital contact tracing has successfully complemented traditional tracing methods by using smartphone application technology to identify exposed social contacts, particularly if they are strangers (Rodríguez et al., 2021). To augment traditional approaches, countries such as South Korea, China, and Singapore have implemented digital contact tracing strategies that are regarded as having contributed to successfully controlling spread (Lancet Digital Health, 2020). Modeling studies suggest that digital contact tracing can break chains of transmission (Salathé et al., 2020), but robust evidence for its effectiveness in real-world outbreak settings is currently lacking (Anglemyer et al., 2020). Widespread implementation of this approach has been hindered by poor integration of the technology with existing surveillance tools (Anglemyer et al., 2020) and by ethical and legal concerns, particularly around privacy, that can undermine public trust and discourage uptake.

The public health benefit of these digital tools in outbreak responses needs to be further explored and better understood, especially for unintended consequences. In addition to the lack of evidence for real-world effectiveness, serious concerns remain that providing access to private information about health, behavior, and location can violate a user's privacy—especially if these do not follow the critical principle of confidentiality and are repurposed for illegitimate surveillance purposes—as well as autonomy, if such technology is mandated (Gasser et al., 2020). Without deliberate investment and incentives to develop appropriate privacy preserving technologies for surveillance and contact tracing, this field will not advance as needed due to fear and ethical questions. Mistrust in these technologies would be a barrier to effective implementation and use. If digital technology is thus used at national or global scale during epidemics or pandemics, developing and instituting best practices and standards for responsible data collection and processing will be critical for engendering public trust (Ienca and Vayena, 2020). Moreover, many settings lack the capacity for local-, national-, and international-level data transmission and sharing through electronic platforms (Gao et al., 2020; Holmgren et al., 2020). Some empirical demonstration is beginning to support the potential real-world util-

ity of digital contact tracing during an infectious disease outbreak scenario, however. A population-based study looked at the impact of a digital contact tracing app implemented in the Canary Islands, Spain, during the summer of 2020 (Rodríguez et al., 2021). The app detected around six close contacts per simulated infection—most of whom were strangers—and the technology had relatively high adherence and compliance. Alongside these promising advances was a controversy regarding the United Kingdom's National Health Service application, which, until mid-August 2021, could advise large groups and clusters of people to self-isolate. The use of this geolocator app placed worker shortages and continued COVID-19 related closures in conflict with the government's wide-scale reopening plans (BBC, 2021).

SURVEILLANCE INNOVATIONS

The COVID-19 pandemic has underscored the need to broaden core capacities for surveillance by leveraging technological advances, including crowdsourced data streams, wastewater surveillance, metadata and line lists that link across data streams, and other innovative approaches. To strengthen preparedness and response to future epidemic and pandemic threats, these approaches—if determined to be effective and ethical—should be consolidated and routinized into central systems to complement traditional surveillance. Aligning international strategies for regulating, evaluating, and using digitally enabled public health is a key step toward realizing the full potential of public health in the future (Budd et al., 2020).

Wastewater Surveillance

The discovery that SARS-CoV-2 was present in infected patients' feces and wastewater (Polo et al., 2020) has given rise to innovations in wastewater-based epidemiological surveillance that employ near-source tracking of sewage drains for specific buildings to detect individual cases or small clusters (Hassard et al., 2021). Wastewater surveillance for infectious diseases holds great potential value for population-wide monitoring and enabling detection of early signals of transmission dynamics, particularly when testing capacity is limited or the time to reporting of diagnostic test results is lengthy or delayed (Peccia et al., 2020). A study in Seattle, Washington, compared seven methods for concentrating and recovering SARS-CoV-2 from municipal wastewater and sludge (Philo et al., 2021). Skimmed milk flocculation without Vertrel extraction yielded the most consistent virus detection results and low variability, although the same may not hold in other contexts. Concentration and detection methods need to be appropriately validated for the setting's specific water matrix to evaluate its performance.

Crowdsourcing Surveillance

Crowdsourcing surveillance by compiling lists of suspected, probable, and confirmed cases could enable quick preliminary assessments of epidemic growth, the potential for spread, appropriate periods of quarantine and isolation, and the efficiency of detection based on the current and evolving evidence base. A crowdsourcing approach was implemented in China in January 2020, when Kaiyuan Sun and colleagues compiled individual-level data from patients with COVID-19—which they mined from a Chinese social media network used by health care professionals—with province-level data about daily case counts (Leung and Leung, 2020). The information was synthesized into a crowdsourced line list that was well aligned with the official epidemiological reports released by the national government. In the future, such crowdsourcing strategies could help mitigate the spread of epidemics, dispel misinformation, and counteract the detrimental impacts of geopolitical tensions and nationalistic populations on science-based epidemic control efforts (Leung and Leung, 2020).

Rapid Epidemic Intelligence

Rapid epidemic intelligence draws on open-source data (e.g., news reports, social media) to supplement traditional surveillance methods and enable early detection of epidemic signals, thus supporting early investigation and accelerating the development of diagnostics. Algorithms for clinical syndromes or diseases, machine learning, and artificial intelligence can be used to establish a baseline threshold for detecting abnormal signals. For instance, an open-source epidemic observatory, EpiWatch, was able to detect early signals of pneumonia or severe acute respiratory illness as a proxy for COVID-19 at the outset of the pandemic in China and Indonesia (Kpozehouen et al., 2020; Thamtono et al., 2021). Similar sources of rapid epidemic intelligence include ProMED, Healthmap in the United States, the Global Public Health Intelligence Network (GPHIN) in Canada (Carter et al., 2020), and Epiwabak in Malaysia.

Nowcasting Surveillance

"Nowcasting" is an innovative framework for assessing the current state of an ongoing outbreak or epidemic by leveraging advances in computational and laboratory sciences to elucidate the event's pathogenic, epidemiologic, clinical, and sociobehavioral characteristics; this approach can enhance situational awareness and inform decisions about response efforts (Wu et al., 2021).

Other Surveillance Innovations

Other surveillance-related innovations during COVID-19 have demonstrated success and feasibility. These include innovative partnerships, such as the COVID-19 Healthcare Coalition,[2] data aggregation networks (Budd et al., 2020), blockchain technologies (Idrees et al., 2021; Mashamba-Thompson and Crayton, 2020), artificial intelligence surveillance tools (Allam et al., 2020), and pooled testing (FDA, 2020). Web-based dashboards can serve as dynamic tools for communicating data, informing decision making, and encouraging behavior change (Ivanković et al., 2021). Harvard has developed a smartphone app that detects loss of taste and smell, a strong indicator of COVID-19 (Hassard et al., 2021). WHO has explored using dogs to screen for COVID-19 (WHO, 2021a).

CONCLUSIONS AND RECOMMENDATIONS

Detection of Potential Threats

Conclusion: COVID-19 has further emphasized the need to use the One Health approach to better target surveillance, including by building on currently existing platforms for influenza surveillance in wild birds, poultry, and livestock. This includes programs for detection of new zoonotic strains with pandemic potential and large antigenic drifts and shifts and research to better understand the pandemic potential of new strains.

Conclusion: One Health programs need to identify new viral strains, assess the risk they pose to people, and analyze where cases are likely to be found and outbreaks are likely to begin. Interdisciplinary collaboration among U.S. agencies, academic institutions, national governments, and multilateral partners has been successful in performing this surveillance in several countries with a One Health approach.

Recommendation 2-1: The World Health Organization, the World Bank, and regional public health organizations should work collaboratively with countries (particularly 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 to develop and support interagency One Health platforms.

[2] For more on the COVID-19 Healthcare Coalition, see https://dsd.c19hcc.org (accessed August 20, 2021).

Quantifying the Spread of a Pandemic

Conclusion: Data informing public health surveillance, including for influenza and COVID-19, are vulnerable to ascertainment biases and therefore may not reflect the true underlying epidemiology; these biases happen particularly as a novel strain is first emerging. When the means used to collect data cannot be changed to avoid these problems, they can be taken into consideration during the analysis and interpretation of data being used to inform policy decisions. If not corrected, these biases can misinform the public about a disease's impact and the likely effects of public health interventions in general and in particular subgroups.

Conclusion: Within countries, the sharing of data collected from community-based surveillance is critical for identifying the likely impact of outbreaks. Inefficiencies in collecting and sharing all types and sources of data among countries and global health agencies hampered the flow of information during the COVID-19 pandemic. The rapid sharing of a wide range of data internationally, including syndromic, epidemiologic, clinical, pathogen specific (e.g., genomic), and other (such as open-source intelligence), can provide early warning of an outbreak of concern as well as a picture of how it may develop.

Recommendation 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, notify authorities to take these biases into account, and seek support for improving surveillance methods to better achieve representativeness and sufficient geographical coverage.

Tracing the Arrival and Community Transmission of a Virus

Conclusion: COVID-19 showed that countries and intergovernmental bodies need to bolster their surveillance capacities, especially the ability to look for the unexpected and unobserved and to sustain surveillance during disease surges. These systems can be strengthened

by being repeatedly challenged to assess their ability to detect novel threats. Gaps identified can then be followed through and retested iteratively before an actual incident. Current surveillance approaches and tools are designed and more suitable for monitoring of known pandemics or the ongoing surveillance for seasonal influenza than for the early detection of a pandemic-capable pathogen before widespread transmission.

Conclusion: COVID-19 showed that the set of core capacities should be broadened to take advantage of technological developments, including but not limited to, digital mobility data, sewage surveillance, and monitoring of open-access electronic data streams (digital surveillance), as well as to maintain a stockpile of basic supplies (such as nasal swabs) that will be needed to conduct tests).

Full reporting of surveillance data, both to higher authorities within a country and to international agencies, is sometimes impeded by negative political or economic repercussions. For example, disciplining local officials for reporting novel pathogens disincentivizes health surveillance. The first step in eliminating such barriers is to recognize their existence; such recognition can come from the parties involved or from observers. Unless such barriers are removed, reporting structures cannot provide complete, accurate, and timely information about possible disease outbreaks.

Harmonization of information from multiple data sources is essential for quickly identifying the origins and spread of novel agents and strains and for providing useful information for decision makers and the public. Harmonization rests on the development and use of instruments to standardize the data. When diverse data come from many sources and reflect clinical and public health differences at the local level, particularly in the early stages of a pandemic, organizations that collect the data may be able to develop means of standardizing the data after they have been submitted.

Recommendation 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.

Recommendation 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.

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3

Effectiveness of Non-Vaccine Control Measures

During epidemics and pandemics of respiratory viruses, non-vaccine public health control interventions have been implemented in diverse settings across the world to reduce viral transmission and curb the spread of disease. This chapter provides a high-level overview of the available evidence regarding the effectiveness of such interventions during the coronavirus disease 2019 (COVID-19) pandemic. The aim is to analyze lessons that can be applied toward strengthening influenza preparedness—including individual-level actions, building and environmental controls, and government and public health controls—rather than offering an exhaustive or comprehensive review. The overview highlights relevant findings and scientific evidence gleaned from research conducted on various measures primarily during COVID-19 and on related types of respiratory virus events. Based on expert guidance, this overview draws from a range of different research domains and methodologies but predominantly relies on studies that show reduced basic reproduction number (R_0), such as randomized controlled trials (RCTs) and systematic reviews, and on laboratory and physical modeling studies that quantify the extent to which specific interventions (e.g., masks, portable air filtration units) can prevent the spread of a virus. It also includes evidence from natural experiments that produce data on interventions being used at varying rates in different settings.

The research strategy for this analysis accounts for the wide variability in the optimal way to assess the evidence available for each type of non-vaccine control measure that was evaluated. For medical and public health research, evidence generated from RCTs is typically considered the gold standard (Greenhalgh, 2020; Pearson, 2021). However, some relevant pub-

lic health interventions cannot be tested using RCTs because it is unfeasible (e.g., national border closure) or unethical in contravening the core tenets of public health, warranting ecological or observational studies to evaluate their effectiveness. Certain fields, such as aerospace engineering, maintain a very low tolerance for error yet rely on laboratory and modeling tests and systematic experimentation. The COVID-19 pandemic has not allowed for many RCTs or trials of any kind, so many policies have had to be based on modeling predictions. For instance, many of the most informative analyses of the impact of face masks, ventilation, and airflow on aerosolized virus transmission come from fundamental principles and research in science and engineering. This pandemic has also illustrated the importance of multidisciplinary study and incorporating lessons and understanding from other fields that do not conduct RCTs, such as industrial hygiene and aerosol science, previously not often included in pandemic planning and response. This is an opportunity to open the framework of public health policy to the broader set of tools of the scientific method from both the medical and biological perspective and rigorous and error-averse classes of physical sciences. This chapter defines evidence for effectiveness as a measure's ability to reduce virus transmission and primarily explores effectiveness in this regard. Chapter 4 will explore the various contextual factors that can affect the population's implementation and optimization of such measures and thereby play into whether particular measures should be recommended for certain settings.

ECONOMIC IMPLICATIONS OF NON-VACCINE CONTROL MEASURES

The economic implications of implementing non-vaccine measures alone to control the COVID-19 pandemic remain largely unquantified. However, a study examined the potential health and economic impacts of mass vaccination in the United Kingdom and showed that with lower-efficacy vaccines, non-vaccine measures will be required long term (over 10 years) (Sandmann et al., 2021). In the best-case scenario, mass immunization with a 95 percent efficacious vaccine, coupled with physical distancing measures, was predicted to yield incremental net monetary values of £12.0–£334.7 billion. Furthermore, community transmission would be minimized without the need for future increases in physical distancing measures. An economic evaluation indicates that lockdowns and physical distancing reduce economic losses, contrary to a prevailing view that such public health pandemic-control measures necessarily undermine economic protection and recovery efforts (MacIntyre, 2021). A modeling study in Australia found the economic costs of an early, mandated lockdown in March 2020 to be multiple times less compared to no interventions (Kom-

pas et al., 2021). An analysis of Portuguese data found that the costs of scaling up COVID-19 testing would be lower than hospitalization costs in most scenarios (Sousa-Pinto et al., 2020), while another study determined that for every euro spent on testing, seven euros would be returned in terms of saved health care expenditures (González López-Valcárcel et al., 2021). A Ugandan cost–benefit analysis found the per capita compounded cost of providing face masks to be around USD 1.34 per Ugandan versus USD 4.00 for medical treatment per individual who becomes infected, possibly due to not wearing a mask (Nannyoga et al., 2020). While the evidence is limited, non-vaccine measures, particularly masks, likewise have been suggested to be cost-effective for seasonal and pandemic influenza (Howard et al., 2021; Mukerji et al., 2015; Tracht et al., 2012).

EVIDENCE FOR INDIVIDUAL-LEVEL ACTIONS

A number of non-vaccine interventions rely on individual actions that have played a pivotal role in reducing the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Such actions have included face masks, appropriate hand hygiene, and different physical distancing measures. However, a discussion of these measures without supportive effective risk communication, health education, and community engagement is likely to achieve suboptimal impacts regardless of the intervention proposed. Chapter 4 discusses more on these important contextual factors.

Face Masks

Laboratory studies, RCTs, and observational studies have demonstrated the effectiveness of face coverings in reducing the transmission of SARS-CoV-2; this impact is believed to apply to influenza as well (Cowling et al., 2009). However, in a real-world setting, the effectiveness of different types of masks varies widely and is largely dependent on the wearer ensuring an appropriate fit. During COVID-19, the World Health Organization (WHO) issued guidance and standards for face masks to achieve appropriate filtration, breathability, and fit (WHO, 2020a) and recommended that masks should have three layers of fabric, including an inner layer of absorbent material, a middle layer of nonwoven nonabsorbent material, and an outer layer of nonabsorbent material (WHO, 2020a).

The National Academies conducted a Rapid Expert Consultation on the Effectiveness of Fabric Masks for the COVID-19 Pandemic in April 2020; despite limited experimental studies available at the time, it highlighted important considerations. Studies showed that a variety of masks reduced emissions of droplets generated by speech (NASEM, 2021), cloth and surgical masks reduced exhaled particle emissions (by one-fifth and

one-half, respectively) (van der Sande et al., 2008), and homemade masks and surgical masks reduced the number of large-sized microorganisms expelled while coughing (Davies et al., 2013). Authors of the rapid expert consultation acknowledge the limited real-world evidence for different types of homemade fabric masks, but laboratory evidence suggests they can reduce transmission of larger respiratory droplets, although the level of protection will be influenced by the user's behavior.

Laboratory and Modeling Studies

A laboratory study of 32 materials used in cloth masks (i.e., cotton, wool, synthetic, synthetic blends, synthetic/cotton blends) with nanometer-sized aerosol particles, found that the five best-performing materials, in terms of filtration efficiency and differential pressure, were three woven 100-percent cotton samples with high-to-moderate yarn counts and two woven synthetics with moderate yarn counts (Zangmeister et al., 2020). In another laboratory study of 44 homemade face-mask materials, decent filtration efficiencies were achieved over a large range of particle sizes by stacking an adequate number of fabric layers and ensuring good fit to reduce leak flows (Drewnick et al., 2021). Similarly, a laboratory evaluation of 11 face coverings determined that a well-fitting three-layer mask with an outer layer of flexible, tightly woven fabric and an inner fabric layer designed to filter particles could provide a minimum of 70 percent filtration efficiency against the most penetrating particles (~0.3 μm) (Pan et al., 2021). Likewise, a study of different fabrics for source control of a human-generated sneeze found that a three-layer mask could outperform a surgical mask and that machine washing did not significantly affect performance; hydrophilicity/wettability of the materials should also be considered (Bhattacharjee et al., 2021). Moderate evidence from laboratory studies with patients suggests that surgical masks also reduce aerosol shedding of seasonal influenza virus (Leung et al., 2020; Milton et al., 2013).

A spate of recent studies from the perspective of fluid dynamics has also demonstrated the efficacy of masks. Computational fluid dynamics simulations have shown that masks can limit the spread of respiratory emissions while also offering some protection to the wearer (Dbouk and Drikakis, 2020; Khosronejad et al., 2020). Visualization using laser sheets has shown that well-fitted masks with multiple layers and those with extra space in front of the nose and mouth were more effective than loose masks in limiting droplet dispersal (Verma et al., 2020).

Together, these studies show that a mask's fit is critical to its performance. Good design (choice of material, configuration and number of layers, antimicrobial activity) can greatly improve performance (Brooks et al., 2021; Pan et al., 2021; Rothamer et al., 2021). The best-performing masks

feature multiple layers of material, excellent filtration capabilities of at least one of the layers, and a tight fit with no leaks. Other factors to consider include breathability, durability, cost, and reuse.

Randomized Controlled Trials and Observational Studies

A meta-analysis of 10 RCTs on community-based use of masks in reducing influenza transmission found no evidence of substantial effect, although it did recommend that masks be worn by symptomatic and uninfected persons during severe epidemics and pandemics (WHO, 2019). However, a systematic review of 172 observational studies across 16 countries and 6 continents that looked specifically at the risk of infection with beta-coronaviruses (e.g., SARS, SARS-CoV-2, Middle Eastern respiratory syndrome-related coronavirus [MERS-CoV]) found that physical distancing of greater than or equal to 1 meter was associated with a substantial reduction in infection, with additional benefit conferred by face masks and eye protection (Chu et al., 2020). Moreover, according to a rapid systematic review of 19 RCTs, community-based mask use appeared effective in reducing the risk of respiratory virus infection even without appropriate hand hygiene, although the combination of measures would likely be more effective (MacIntyre and Chughtai, 2020). Although a Danish RCT conducted early in the COVID-19 pandemic found no statistically significant difference in infection rates between users randomly assigned to a recommendation of face masks and controls (Bundgaard et al., 2020), the results were met with debate. It was argued that the study did not account for the role of mask use in reducing transmission to others (Abbasi, 2020) and only examined the effect of recommending mask use, rather than actually wearing masks (Laine et al., 2021).

Mask Mandates

The COVID-19 pandemic has featured increasing calls to implement national- or local-level mask mandates. Modeling has suggested that requiring mask use by the entire public, not just symptomatic individuals, could achieve a median effective R_0 of below 1, even with mask effectiveness of just 50 percent (Stutt et al., 2020). These findings are supported by a mathematical modeling study in Victoria, Australia, that illustrated how rates of mask use greater than 50 percent can substantially improve epidemic control, even without other measures (e.g., lockdowns) and with masks offering low-to-moderate protection (Costantino et al., 2020). In the United States, implementation of mask mandates has been linked to decreases in daily COVID-19 case and death growth rates within 20 days (Guy et al., 2021b). Thirteen U.S. states that reopened with mask mandates in spring

2020 prevented an estimated 50,000 excess deaths within 6 weeks; excess cases and excess deaths could have been reduced from 576,371 to 63,062 (about 90 percent) and from 22,851 to 4,858 (about 80 percent), respectively, within 6 weeks had other states implemented mask mandates before reopening (Kaufman et al., 2020). An analysis of mask use in the United States, the United Kingdom, and Australia found mandates to be predictors of mask wearing (MacIntyre et al., 2021), and a study of U.S. states with the lowest mask adherence were found to have the highest COVID-19 rates (Fischer et al., 2021), further suggesting that mask mandates may be effective in reducing virus transmission.

Mask mandates have also been found to reduce transmission amidst restaurant reopening during COVID-19: an increased risk of cases was attenuated by up to about 90 percent and deaths up to 80 percent in U.S. states that implemented statewide mask mandates prior to reopening restaurants for indoor dining (Guy et al., 2021a). An analysis in Hong Kong during a mask mandate found that most COVID-19 transmission occurred in mask-off settings, such as households and restaurants, supporting the effectiveness of masks (Martín-Sánchez et al., 2021).

Face Shields

Face shields are infection control measures widely used during the COVID-19 pandemic, often in lieu of face masks. Although face shields are designed to be worn over a mask in health care settings, they are not meant to serve as sole respiratory protection. However, they are often used under the mistaken presumption that SARS-CoV-2 and other respiratory viruses spread through ballistic strikes with large droplets rather than inhalation of aerosols. Face shields can protect the eyes from ballistic strikes, but they will not reduce inhalation exposure. In addition, evidence suggests they are not effective. These findings are valid for aerosols of any type, so they are expected to apply to influenza viruses carried in small aerosols. In laboratory studies, a face shield blocked the emission of just 2–4 percent of total cough aerosols, much less than other types of face coverings (Li, L. et al., 2020a; Lindsley et al., 2020). A study with coughing patient and breathing worker simulators found that although face shields can be useful adjuncts, they cannot substitute for respiratory protection (e.g., face masks) against influenza-laden aerosols (Lindsley et al., 2014), which is the general guidance for health care workers (Roberge, 2016).

Hand Hygiene

Hand hygiene is another frequently used intervention against respiratory viruses, despite relatively little evidence of its effectiveness. A

systematic review of RCTs found that hand hygiene did not appear to have a substantial effect on the transmission of laboratory-confirmed influenza—based on a moderate quality of evidence—although mechanistic studies have shown that it can deactivate or remove influenza virus from hands (WHO, 2019). An evaluation of Taiwan's early response to the COVID-19 pandemic suggests that universal hygiene—including handwashing—and mass masking contributed to a 50 percent decline in infectious respiratory illnesses, including COVID-19, influenza, and influenza-like illnesses (ILIs) (Hsieh et al., 2020). The results of a randomized trial in university residence halls during influenza season suggest that the combination of hand hygiene and face masks significantly reduced the incidence of ILI in shared living spaces (Aiello et al., 2010). In Hong Kong, masks plus hand hygiene were protective if used early, but hand hygiene alone was not (Cowling et al., 2009). During the 2009 influenza A (H1N1) outbreak in Bangkok, Thailand, a study of influenza virus contamination in homes with an infected child found that increased handwashing was not associated with protection, despite an earlier study showing that the hands of children with influenza were contaminated with the virus (Simmerman et al., 2010). However, like masks, it is important to track the details of hand hygiene, as these impact its effectiveness. More research is needed to assess the efficacy of interventions such as handwashing, coupled with ventilation of common facilities, such as restrooms, where handwashing takes place.

Physical Distancing Measures

Physical distancing reduces the risk of respiratory virus transmission by positioning people beyond the range of large, ballistic respiratory droplets and away from high concentrations of aerosol particles in a freshly emitted respiratory plume. The optimal distance remains a matter of debate, although the emerging scientific view is that no universal safe distance is applicable to specific pathogens, especially when considering physical activity, occupancy level, and characteristics of the built environment. During the COVID-19 pandemic, guidance from WHO and many national governments recommended physical distancing of 1.5–2 meters to reduce airborne transmission. However, a narrative review has proposed that recommendations of 1–2 meters are premised on outdated assumptions about respiratory droplet size and may neglect factors that affect the distribution of viral particles, such as airflow, ventilation, and the means and frequency of expulsion (Jones et al., 2020). A range of 1–2 meters is also impractical, as it is not specific enough. Respiratory droplets of up to 60 μm in size have been shown to travel a horizontal distance of more than 2 meters, suggesting that SARS-CoV-2 could

achieve such distances during coughing or shouting (Bahl et al., 2020). Aerosols, of course, can travel much farther, carried by air currents. Other research has supported the hypothesis that SARS-CoV-2 can be transmitted beyond a distance of 2 meters, due to its higher aerosol and surface stability (Setti et al., 2020). A systematic review of 172 observational studies from 16 countries suggests that physical distancing greater than 1 meter was associated with a lower beta-coronavirus transmission than distancing less than 1 meter; protection increased up to 3 meters, which was the longest distance for which data were available (Chu et al., 2020). However, these evaluations did not account for local airflow patterns; distancing without doing so cannot evaluate the role of distancing as a control measure beyond 1 meter.

A Rapid Expert Consultation on Social Distancing During the COVID-19 Pandemic conducted by the National Academies in March 2020 also highlighted the effectiveness of physical distancing (NASEM, 2021). Much of the evidence was based on previous influenza experience and found that it is not always well defined but is generally most effective when implemented early. A study in Wuhan noted that the reproductive number dropped from 3.86 to 1.26 following the introduction of several physical distancing measures (Wang et al., 2020). However, implementation matters. Additional modeling exercises from Imperial College London suggested that a 3-month period of intervention stressing distancing could reduce deaths by half and health care demand by two-thirds. But if only half measures were put into place (i.e., only elderly people versus the whole population), the epidemic could overwhelm health systems in the United States and lead to more than 1 million deaths (Ferguson et al., 2020).

A natural experiment across 149 countries and regions found that implementing any type of physical distancing intervention was associated with a 13 percent overall reduction in COVID-19 incidence in the pandemic's early months (Islam et al., 2020). However, an observational study in the United Kingdom suggests that current physical distancing measures in schools are insufficient to combat the spread of rhinovirus, influenza, and potentially SARS-CoV-2 (Poole et al., 2020). Drawing largely from observational and simulation studies, a systematic review of physical distancing measures found that they could be effective during a pandemic in terms of reducing transmission and mitigating overall impact (Fong et al., 2020).

A summary of the evidence of various individual measures explored in this chapter (see Table 3-1) and a list of potential research topics that need additional study in this area (see Box 3-1) are outlined below.

TABLE 3-1 Individual-Level Measures: Evidence Supporting Efficacy/Effectiveness* in Reducing Transmission of Respiratory Viruses

Individual Measures	Strength of Evidence	Effectiveness/ Efficacy	Summary of Evidence (with Citation)
Face masks	Strong	High	• Properly designed, well-fitting masks with multiple layers of material and strong filtration capacity are effective in reducing droplet and aerosol shedding in laboratory studies (Brooks et al., 2021; Milton et al., 2013; Pan et al., 2021; Rothamer et al., 2021). • A rapid systematic review of 19 RCTs showed that community-based mask use appeared effective in reducing the risk of respiratory virus infection (MacIntyre and Chughtai, 2020). • Mask mandates were linked to a decrease in the daily growth rate in COVID-19 cases and deaths within 20 days of implementation (Guy et al., 2021b).
Physical distancing	Strong	Moderate	• A systematic review of distancing measures found that they could be effective in reducing transmission; protection against infection began at a distance of 1 meter and increased incrementally to 3 meters (Chu et al., 2020). But without accounting for airflow patterns, distancing beyond 1 meter cannot be evaluated. • An integrated risk assessment of close proximity exposure to SARS-CoV-2, based on fluid dynamics modeling, showed that the risk of transmission decreased with distance (Cortellessa et al., 2021).
Hand hygiene	Low to moderate	Low to moderate, except when combined with masks or respiratory hygiene	• Data are mixed for hand hygiene by itself. One pre-COVID-19 meta-analysis suggested hand hygiene affords 16 percent protection (Jefferson et al., 2020), but a systematic review of trials of masks and hand hygiene found that hand hygiene alone was not effective (MacIntyre and Chughtai, 2020). Other trials have shown no effect of hand hygiene alone on specific respiratory viruses, including rhinovirus and influenza (Cowling et al., 2009; Turner et al., 2012).

continued

TABLE 3-1 Continued

Individual Measures	Strength of Evidence	Effectiveness/ Efficacy	Summary of Evidence (with Citation)
Hand hygiene (continued)			• Studies suggest that hand hygiene may provide benefit when used in combination with other interventions, such as masks, including for respiratory viruses in which contact transmission is a major factor. The evidence suggests a decline in infectious respiratory illnesses, including COVID-19, influenza, and ILIs, when hand hygiene is combined with mass masking (Aiello et al., 2010; Hsieh et al., 2020). A large trial that combined respiratory and hand hygiene showed reduction of influenza A but not all types and strains of influenza (Stebbins et al., 2011).
Face shields	Moderate	Low, when used alone	• Evidence does not support face shields as replacements for masks or as effective against the inhalation of aerosols (Li, L. et al., 2020; Lindsley et al., 2014, 2020).
	Limited	Moderate, when used with a face mask	• Use of face shields or other eye protection in combination with masking appears to decrease the risk of beta-coronavirus transmission in a systematic review with meta-analysis of studies from health care and community settings (Chu et al., 2020). • A retrospective study of 45 patients in Toronto with SARS-CoV who required intubation found that unprotected eye contact with secretions was associated with increased risk of transmission among treatment personnel (Raboud et al., 2010). • A retrospective observational study of community health workers in India who counseled and tested asymptomatic family contacts of persons diagnosed with COVID-19 found that 19 percent became infected even though they were masked and practiced physical distancing, but after they began also wearing face shields, none were infected, even though the second period involved 12 times as many people in three times as many homes with a positive test (Bhaskar and Arun, 2020).

* "Efficacy" refers to data from RCTs; "effectiveness" refers to data from experimental or observational epidemiologic studies.

BOX 3-1
Examples of Research Topics Related to Non-Vaccine Control Measures Related to Individual Actions

- Explore how individual behavior impacts mask effectiveness in different settings.
- Assess the efficacy of interventions, such as handwashing, coupled with air venting of common facilities, such as restrooms, where handwashing takes place.
- Analyze the impact of airflow, direction, duration of exposure, and masks on the effectiveness of physical distancing.

EVIDENCE FOR BUILDING AND ENVIRONMENTAL CONTROLS

Buildings have been associated with the spread of infectious diseases, such as of influenza and COVID-19, which has highlighted the role of building and environmental controls in reducing transmission during epidemics and pandemics. Measures have included plexiglass barriers, ventilation and filtration systems, ultraviolet (UV) inactivation, ionization, and surface cleaning, but the availability and quality of evidence for their effectiveness varies widely.

Barriers

The effectiveness of barriers, such as clear plastic, as infection control measures has not yet been investigated directly, but a 2013 study of physical partitions between beds in a hospital ward found that airborne pathogen infection risk was not reduced; it merely shifted to different rooms (Gilkeson et al., 2013). Desk shields in schools have been found to be associated with increases in the risks of COVID-19-related symptoms (Lessler et al., 2021). In some situations, barriers, whether plexiglass or otherwise, could be helpful in mitigating transmission, such as clinical or other visits where there are just two people in a room. However, for this to be effective, proper ventilation is correspondingly required to remove aerosols that are diverted by the barriers. A study measuring barrier efficiency for worker protection found that a barrier that blocked an initial cough from a simulator was effective at reducing particle counts, but the height of the barrier was more significant than the width in determining efficiency (Bartels et al., 2021). However, barriers can create “hot spots” in a room and increase exposure to those who may be nearby, so it is important for airflow in the room and ventilation to be considered as well.

Ventilation and Filtration

Science and engineering research has linked poor ventilation with increased risk of transmission of respiratory pathogens. Similarly, observational and modeling studies of tuberculosis (TB) over previous decades have also shown the influence that ventilation can have on outbreaks. For example, modifications to improve cross-ventilation and open air in hospitals in Peru resulted in a median 72 percent reduction in calculated TB transmission risk (Escombe et al., 2019). A study in Taiwan measured the effect of improving ventilation rate on a TB outbreak in less ventilated university buildings and found that levels with carbon dioxide less than 1,000 ppm was associated with a 97 percent decrease in TB incidence among contacts (Du et al., 2020).

Most outbreaks of COVID-19 involving at least three people have been associated with time spent indoors, highlighting the importance of good ventilation (Allen and Ibrahim, 2021). SARS-CoV-2 can be spread through "far-field" airborne transmission within the same room but over distances greater than 2 meters (Allen and Ibrahim, 2021). In March 2020, poor ventilation was implicated in the superspreading event for the Skagit Valley chorale in the U.S. state of Washington, which was likely exacerbated by generating large volumes of respiratory aerosolized virus during singing (Miller et al., 2021). Similarly, airborne spread of SARS-CoV-2 was also shown to be likely in a church outbreak involving singing in Australia, despite physical distancing; cases occurred in people who were up to 15 meters away from the index case with no close physical contact (Katelaris et al., 2021). As all secondary cases were seated in a certain section behind the singer, this study illustrated the importance of airflow direction.

Inadequate ventilation has also been regarded as contributing to outbreaks within nursing homes (de Man et al., 2020) and restaurants (Li, Y. et al., 2020; Lu and Yang, 2020). An analysis of an incident in which three individuals caught SARS-CoV-2 in a restaurant in South Korea found that with direct airflow from a person who is infected, droplet transmission can occur over distances greater than 2 meters (Kwon et al., 2020). An investigation of 169 schools in the U.S. state of Georgia found that improved ventilation by opening windows and doors or using fans was associated with a 35 percent lower incidence of COVID-19 among students and staff (Gettings, 2021).

In health care, office buildings, apartments, and other high-occupancy settings, routes of airflow and ventilation should be considered in strategies to mitigate risk of airborne transmission of respiratory viruses. In a randomized human-challenge influenza transmission study, the secondary attack rate was significantly lower than expected based on the preceding proof-of-concept study, with mechanical building ventilation in the follow-

on study being the main variable (Nguyen-Van-Tam et al., 2020). A study examining building ventilation and laboratory-confirmed acute respiratory infections was conducted in two U.S. university residence halls, one with high ventilation—via a dedicated outdoor air system supplying 100 percent of outside air to each room—and one with low ventilation relying on infiltration (Zhu et al., 2020). Residents in the former were found to have much lower incidence of acute respiratory infection during the study period (1 case versus 47 cases). Opening both windows and doors in the low-ventilation building increased ventilation rates roughly to the level of the high-ventilation building.

Air cleaners, when properly installed to account for space and airflow, represent a simple, cost-effective intervention for reducing aerosol transmission. In a COVID-19 ward at a hospital in Melbourne, Australia, a study of the transmission of aerosols from a patient room into hallways and a nurses' station found that aerosols traveled rapidly. However, air cleaners (i.e., portable high-efficiency particulate air [HEPA] filters) increased the clearance of aerosols from the air and reduced their spread: two small air cleaners can clear 99 percent of aerosols from a patient room within about 5 minutes (Buising et al., 2021). Similarly, an analysis of the use of four HEPA-filter air purifiers (air exchange rate 5.5 h^{-1}) in a high-school classroom in Germany found that they reduced the aerosol number concentration by greater than 90 percent within 30 minutes in a room with doors and windows closed, thus substantially reducing the risk of SARS-CoV-2 transmission (Curtius et al., 2021). In a study of schools in the U.S. state of Georgia, HEPA filtration in addition to ventilation improvements were associated with a lower incidence of COVID-19 compared to ventilation improvements alone (Gettings, 2021). Filtration and ventilation with outdoor air are complementary tools. Optimizing their application depends on the specifications of the heating, ventilation, and air conditioning (HVAC) system, outdoor air quality, and other factors. For example, when areas are impacted by wildfire smoke, people should not rely on ventilation with outdoor air. On the other hand, increasing the quality of filters in an HVAC system can lead to reduced ventilation rates or place strain on the equipment. HEPA filters should be maintained and replaced in accordance with the system's guidance to ensure optimal system function and reduce strain (Zhao et al., 2020).

Ultraviolet Inactivation and Ionization

UV germicidal air disinfection is an engineering method that can be used to control the transmission of airborne pathogens in high-risk environments (Walker and Ko, 2007). A laboratory study demonstrated that 254-nm ultraviolet germicidal irradiation (UVGI) may be an effective measure

to prevent the transmission of respiratory viral diseases (Walker and Ko, 2007). Furthermore, research has shown SARS-CoV-2 specifically to be inactivated by UV (Heilingloh et al., 2020). The design of a UVGI system is critical in optimizing its performance. A simulation study reported that both ceiling height and mounting height of UVGI fixtures in hospital rooms can contribute to variation in upper-zone fluence rate of up to 22 percent (Hou et al., 2021). The study also demonstrated that interreflections within a room should be considered when designing UVGI fixture placement in the upper part of a room, to avoid creating "hot spots" where a room's occupant could be in danger of being overexposed to UV in the lower part. Effective application of UVGI also requires adequate analysis of airflow and flow dynamics of the room to avoid creating areas with high pathogen concentrations.

Claims for the efficacy of ionization have not been independently verified (Zeng et al., 2021). Furthermore, ionization may cause harmful byproducts and has not been recommended by the U.S. Centers for Disease Control and Prevention (CDC) or the American Society of Heating, Refrigerating, and Air-Conditioning Engineers.

Surface Cleaning

Evidence is weak to nonexistent that measures such as surface cleaning are effective in reducing the transmission of SARS-CoV-2. According to U.S. CDC, the risk of fomite-mediated transmission considered relatively low compared to direct contact, droplets, or airborne transmission (CDC, 2021b). Quantitative microbial risk assessment studies on the relative risk of SARS-CoV-2 fomite transmission suggest that the risk from coming into contact with a contaminated surface is just 1 in 10,000 (CDC, 2021b). A study conducted in intensive care units (ICUs) treating COVID-19 patients found that basic cleaning with standard disinfection measures was sufficient to eliminate SARS-CoV-2 RNA from surfaces (Hofmaenner et al., 2021). However, during biweekly virus monitoring in four U.S. primary school classrooms, greater than 20 percent of the school desks sampled had detectable DNA and RNA from respiratory viruses and norovirus. Based on the occurrence patterns, if more than five desks were occupied per day, the room occupants had a greater than 60 percent chance of encountering any virus, most commonly rhinoviruses and adenoviruses (Zulli et al., 2021). Additionally, the relation between surface type and property matter remain poorly understood (Otter et al., 2016).

A summary of the evidence of various building and environmental control measures explored in this chapter (see Table 3-2) and a list of potential research topics that need additional study in this area (see Box 3-2) are outlined below.

TABLE 3-2 Building and Environmental Control Measures: Evidence Supporting Efficacy/Effectiveness* in Reducing Transmission of Respiratory Viruses

Environmental Measure	Strength of Evidence	Efficacy/ Effectiveness	Summary of Evidence (with Citation)
Ventilation and air filtration	Moderate	Moderate effectiveness	• Air cleaners were shown to remove 99 percent of aerosol particles in a COVID-19 ward in a Melbourne hospital (Buising et al., 2021). • Poor ventilation has been associated with SARS-CoV-2 outbreaks in nursing homes (de Man et al., 2020), restaurants (Li, Y. et al., 2020; Lu and Yang, 2020), and a choir practice (Miller et al., 2021).
UV irradiation	Low	Moderate efficacy	• Laboratory studies have suggested the effectiveness of UV in inactivating SARS-CoV-2 on surfaces (Heilingloh et al., 2020).
Ionization	Low	Low efficacy	• Laboratory and field testing indicated no significant reduction in particle number and mass concentrations (Zeng et al., 2021). • Ionization may generate harmful by-products, and its clinical effectiveness has not been verified (Zeng et al., 2021).
Surface cleaning	Moderate	Low for SARS-CoV-2 but can be moderate, depending on the pathogen	• Little evidence supports surface cleaning as an effective method to reduce transmission of SARS-CoV-2, because it seems to be mediated primarily by direct contact, droplets, or airborne transmission (CDC, 2021b). ° For other respiratory viruses, such as respiratory syncytial virus, with a higher risk of fomite or surface transmission, surface cleaning may have increased importance (Krilov, 2001). Additionally, the relation between surface type and property matter remain poorly understood (Otter et al., 2016).
Barriers	Low	Low	• Few studies exist on the effectiveness of barriers. • A 2013 study found that airborne pathogen infection risk was not eliminated by barriers in hospital rooms but merely shifted to different rooms (Gilkeson et al., 2013). • More recent evidence suggests that in certain settings, barriers may be counterproductive; in schools, barriers on desks were shown to be associated with increased risk of COVID-19-related symptoms (Lessler et al., 2021).

* "Efficacy" refers to data from RCTs; "effectiveness" refers to data from experimental or observational epidemiologic studies.

BOX 3-2
Examples of Research Topics Related to Non-Vaccine Control Measures for Building and Environmental Controls

- Examine how airflow and ventilation impact the effect of barriers, such as clear plastic shields, on transmission in different settings.
- Gather more data on the efficacy of ionization and its potential to generate harmful by-products.
- Analyze the persistence of virus infectivity on various surface types.

EVIDENCE FOR GOVERNMENT AND PUBLIC HEALTH CONTROLS

Governments and public health agencies have instituted a number of restrictions and mandates to control the spread of COVID-19. Although these controls have demonstrated effectiveness in reducing virus transmission overall, they have other potential implications that could have bearings on future influenza preparedness efforts. These measures have included travel restrictions, lockdowns, and mandates for curfew, school and business closures, testing, and quarantine. However, instituting and enforcing these measures without supportive and effective risk communication, health education, and community engagement in advance is bound to achieve suboptimal impacts. Adding to the complexity is the ongoing learning curve regarding household transmission for initial COVID-19 strains and emerging variants. Regardless of the type of measure, it is important for researchers and policy makers to understand the mode of transmission to be able to best inform when certain measures are implemented and in what settings. When the pandemic began in early 2020, a study of the wild-type SARS-CoV-2 found that patients had the highest viral load in throat swabs at the time of symptom onset, with an estimated 44 percent presymptomatic transmission (He et al., 2020). This helped fuel policies such as temperature checks and ensuring people stayed home when sick. However, in a study in summer 2021 examining the transmission dynamics of the Delta variant in an outbreak in southern China, researchers found that those infected with the variant had a more rapid symptom onset (incubation period of 5.8 days) and higher viral load and that nearly 74 percent of the transmissions occurred before symptom onset (Kang et al., 2021). Understanding how the virus spreads from person to person should guide how public health measures are implemented.

Currently, sufficient evidence is lacking for most effective interventions within a household, especially in poorer, crowded environments where

people are more densely living. However, screening programs or free testing may not be successful if there are no guarantees of payment or a safety net if a person tests positive and needs to quarantine for a longer period. Evidence is also lacking on whether the entire household needs to quarantine, and for how long, if one person tests positive. Careful study on this would be helpful in understanding the epidemiology and informing policy decisions and guidance. More on the critical importance of these various contextual factors is also discussed in Chapter 4.

Travel Restrictions

Many countries have enacted non-vaccine control measures related to international travel in response to the COVID-19 pandemic, such as inbound/outbound traveler screening, quarantines, and other travel restrictions. Some countries have even imposed border closures or other stringent border controls, such as banning entry by all non-nationals and, in the case of Australia, even Australian nationals returning to the country from India in May 2021. Such policies can be contentious because they run contrary to International Health Regulations (IHR) advice that nations should avoid closing their borders to avert restrictions on international travel and trade. Because of this, WHO has not recommended border closures during the COVID-19 pandemic (WHO, 2020b). However, some advocates have called for modifying the IHR to be more flexible to allow for limiting international travel and trade at early points in epidemics, where this action could positively influence the outbreak direction (von Tigerstrom and Wilson, 2020). This would ideally be coupled with a fund to support countries that are economically affected by the restrictions and strategies to effectively reopen when appropriate. As various countries have enacted different levels of travel restrictions, it has been clear that some interventions are more successful in certain locations depending on geography, culture, or population. This section outlines the evidence for different types of restrictions on the case count or levels of community transmission, but the contextual factors for where and when these interventions are most successful can be difficult to distinguish, and more understanding is needed.

Evidence for the effectiveness of travel-related restrictions to halt the spread of viral transmission is mixed (Burns et al., 2021; Kang et al., 2020), and it is ecological or observational by necessity. However, evidence around the emergence of variants of SARS-CoV-2 in early 2021 appears to provide some justification for border restrictions from an epidemiological stance (Mallapaty, 2020; Pham et al., 2021). Evidence for reducing virus transmission stands apart from considerations about whether such policies are sustainable and equitable, able to isolate the disease but not the people in the countries with such restrictions, taking into account many factors, such

as ensuring that such measures do not hamper the medical/supply chain and international medical staff supporting countries in the epidemic and pandemic response.

Geography and timing are critical considerations in travel-restriction measures. Countries such as Australia and New Zealand implemented travel bans combined with hotel quarantine of all incoming travelers early in 2020—before community transmission was established—and were able to largely avert the deleterious impacts of COVID-19 experienced by countries that did not do so quickly (Huang et al., 2021). This suggests that island nations may have more success with travel measures than countries with porous national borders, as evidenced by the success of New Zealand's strict border control strategies. As of January 2021, the country had just 2,262 probable and confirmed cases—and 25 deaths—in its population of 5.1 million (Baker et al., 2020). Furthermore, travel bans are only effective before substantial community transmission is established (Cumming, 2021). Modeling studies suggest that Australia's first travel ban for China reduced imported cases by 79 percent, delayed widespread transmission by about 1 month (Adekunle et al., 2020), and averted a larger-scale epidemic by restricting incoming passengers from China when COVID-19 was largely localized in Wuhan (Costantino et al., 2020).

A rapid systematic review of 29 studies reported a high degree of consensus that travel-restriction measures contributed substantially to changes in the dynamics of the COVID-19 pandemic, particularly when implemented during the early phases (Grépin et al., 2021). For instance, immediate restrictions in Wuhan were associated with a 70–80 percent reduction in cases exported to other countries and reductions in transmission within mainland China. Restrictions on flights in and out of China also likely contributed to further reductions in the volume of exported cases. A caveat is that most studies only evaluated international travel measures and did not account for domestic travel measures, potentially biasing their estimates of effectiveness. Moreover, a systematic review of 15 studies found no evidence suggesting that screening inbound travelers would substantially reduce the spread of pandemic influenza; no studies reviewed had evaluated the effect of screening outbound travelers (Ryu et al., 2020).

A rapid review of 40 experimental, observational, and modeling studies on travel-related control measures in response to COVID-19, SARS, and MERS-CoV found a low certainty of evidence for their effectiveness based on cases detected or averted. However, the authors posited that travel restrictions could have a positive impact on certain outcomes. For instance, although evidence for separate measures, such as symptom screening and quarantine, was not sufficient to draw conclusions about their effectiveness when implemented alone, combinations of measures (e.g., screening, observation, testing) would likely improve effectiveness. Evidence from this

study was insufficient to draw conclusive findings about the effectiveness of a quarantine related to travel as a stand-alone control intervention. However, they noted that effects probably depend on factors such as epidemic phase, countries' interconnectedness, and local-level measures to contain transmission (Burns et al., 2020).

Public health measures against COVID-19, particularly border closures, may also reduce transmission of other types of respiratory viruses. In Australia, stringent restrictions on movement within and into the country may have temporarily eliminated influenza in March 2020, when winter approached for the southern hemisphere and Australia was expected to experience high, concurrent levels of SARS-CoV-2, influenza, and other seasonal respiratory viruses. Influenza notifications, hospitalizations, and deaths were substantially lower compared to influenza seasons in previous years, based on national ILI sentinel surveillance and national sentinel hospitalization data (Sullivan et al., 2020). Another study found that Western Australia had huge reductions in the number of cases of respiratory syncytial virus (98.0 percent) and influenza (99.4 percent) among children through winter 2020, despite schools reopening (Yeoh et al., 2020).

Lockdowns and Curfew

Some evidence suggests that government-imposed lockdown and curfew measures may reduce the transmission of SARS-CoV-2 and potentially influenza (Sullivan et al., 2020) but with wide-ranging implications. An evaluation of French Guiana's COVID-19 control strategy found that a combination of interventions, including curfews and targeted lockdowns, was associated with a decline in R_0 from 1.7 to 1.1 (Andronico et al., 2021). A systematic review evaluated the effectiveness of lockdown with or without mass testing in controlling COVID-19 (Johanna et al., 2020). Ten of the studies suggested that lockdowns reduced incidence, onward transmission, and mortality rate, with limited evidence that combining lockdown and mass screening was more effective in reducing incidence and mortality rates than lockdown alone. Insufficient evidence was available to evaluate the effectiveness of mass screening, however.

Stay-at-Home Orders

An evaluation of U.S. physical distancing policies found that statewide stay-at-home orders and limits on restaurants and bars were linked to reductions in out-of-home mobility (15.2 percent and 8.5 percent, respectively) early in the pandemic, but the other policies studied—such as nonessential business closures, limited stay-at-home orders, school closure mandates, and bans on large gatherings—were not, perhaps due to the

benefits of voluntary physical distancing (Abouk and Heydari, 2021). Another study looked at the relationship between confirmed COVID-19 cases and U.S. state or local social distancing measures, including (1) large social gathering bans; (2) school closures; (3) entertainment venue, gym, bar, and restaurant dining area closures; and (4) shelter-in-place orders. The analysis suggests that in March and April 2020, without shelter-in-place orders or any of the four interventions, COVID-19 would have had 10-fold or 35-fold greater spread, respectively (Courtemanche et al., 2020). A natural experiment found that as England transitioned from national lockdown to localized interventions and tiered mitigation strategies, survey respondents tended to report fewer social contacts after each measure was introduced, albeit with small and variable magnitudes of change (Jarvis et al., 2021).

Children/School Closures

School closures have demonstrated effectiveness in curbing community outbreaks of influenza (Bin Nafisah et al., 2018; Jackson et al., 2013; Stebbins et al., 2010), and this strategy has been frequently part of national and local COVID-19 pandemic response. However, it is not likely that sustained school closures are as effective in preventing community spread of COVID-19 as they are for influenza, due to important differences in the age profiles of infectivity and susceptibility (Heald-Sargent et al., 2020). Research has demonstrated that children less than 10 years old tend to have lower levels of infectivity than adults and thus are unlikely to be primary drivers of SARS-CoV-2 community transmission (Bullard et al., 2021; Kim et al., 2020).[1] In contrast, young children represent a major source of influenza transmission because they tend to shed the virus for longer than adults, in both the pre- and post-symptomatic periods (Heald-Sargent et al., 2020; Ng et al., 2016). The age profile of students within a school is another consideration relevant to decisions about school and university closures. For example, emerging evidence suggests that young adults of university age have higher levels of infectivity and susceptibility to COVID-19 than children under age 18. However, with variants, such as Delta, influencing these factors, this may not continue to be accurate. A preprint from the United Kingdom demonstrated that younger groups were driving much of the latest surge in cases, with fivefold higher rates of swab positivity among younger children (5–12 years) and young adults (18–24 years) (Riley et al., 2021). Generally, older adolescents and young adults are thought to represent

[1] As mentioned in Chapter 1, this report reflects the state of the science when it was written in summer 2021. As new strains emerge and data on children's infectivity or susceptibility are obtained, especially related to the Delta variant circulating widely in August and September 2021, that new information may be more accurate.

major vectors of spread for COVID-19, given their greater propensity for social mixing and risky behavior in terms of respiratory pathogen spread (Li, X. et al., 2020; Viner et al., 2021; Wu et al., 2020).

A validated mathematical model of school outbreaks demonstrated that shortening the school week significantly reduced the lengths of both influenza and COVID-19 outbreaks, while post-fever isolation policies were less effective (Burns and Gutfraind, 2020). For influenza, a 1- or 2-day post-fever isolation policy reduced the median attack rate substantially (29 percent and 70 percent, respectively), while shortening the school week reduced the rate by 93 percent for a 3-day week and 73 percent for a 4-day week. For COVID-19, the post-fever isolation policy was much less effective in reducing the attack rate (2 days: 10 percent; 14 days: 14 percent) than a 4-day (57 percent) or 3-day (81 percent) week.

A decision-analytical modeling study attributed most COVID-19 cases in schools to community acquisition rather than within-school transmission. Furthermore, changes in case numbers associated with school reopening were smaller than those linked to community-based non-vaccine control interventions (Naimark et al., 2021). However, at the time of this report, many countries have only just reopened in-person schooling, so evidence is insufficient on the impact of that choice, whether schools are a driver or dominant environment for transmission, and whether children are now bringing home the virus and transmitting to family members. More research in this area is warranted, especially on multigenerational households with certain individuals who may be more susceptible. As many countries begin grappling with how to reopen schools and resume in-person classes, it will be necessary to ensure they have the physical capabilities to do so safely, including water, sanitation, and hygiene services and flexible learning environments. In Senegal and Niger, only 22 and 15 percent, respectively, of schools have access to basic handwashing (UNICEF, 2020). However, while keeping schools closed may keep them safer from the virus, development experts highlight the negative consequences for children's learning in low- and middle-income countries. The longer children are out of school, the more likely they are to drop out and the higher their risk of recruitment by armed groups or early marriages for young girls. It will be important for governments to consider these needs in their pandemic response, including the economic consequences that families face due to business closures. Many families may have trouble finding the money for school fees, so even when reopened, schools may have fewer students to support teachers and other staff. Better understanding of whether schools are driving transmission as they reopen, and what interventions are most effective, especially in low-resource contexts, will be critical to maintaining safe education for millions of children.

Non-School Venue Closures

The impact of closing non-school venues (e.g., bars, restaurants, gyms, entertainment venues) on respiratory virus transmission is difficult to quantify. However, both COVID-19 and influenza are statistically overdispersed—with large proportions of their caseloads attributable to a number of large clusters—which makes communal settings places where substantial numbers of infections could potentially occur. For instance, indoor dining at restaurants is associated with greater risk of transmission, because people eat and drink without masks. U.S. CDC has reported that in March–December 2020, U.S. counties permitting on-premises restaurant dining experienced increases in daily COVID-19 case growth and death growth rates 41–100 days and 61–100 days afterward, respectively (Guy et al., 2021b). A study in Hong Kong showed most transmission occurred in mask-off settings, such as restaurants (Martín-Sánchez et al., 2021). Similarly, a modeling study compared real-time trends in movement patterns based on cell-phone data with the rate of new COVID-19 infections in 25 high-incidence U.S. counties, finding that reduced mobility (i.e., physical distancing) was strongly correlated with decreased case-growth rates in most of the counties (Badr et al., 2020). The overall efficacy of measures such as business closures depends highly on whether the facilities have indoor versus outdoor or combined outdoor-indoor settings. Full closure may not be necessary for those with an outdoor option, but then the season and geographical location will play a role in successful implementation.

Testing

Molecular tests can be effective diagnostics during a pandemic, but they are limited by production capacity and the time needed to obtain results—which is problematic in the context of a highly transmissible virus—although antigenic tests may be able to overcome those challenges. This underscores the need to strengthen testing preparations before a pandemic by considering community-specific factors, such as determining which types of tests to use, ensuring they are available and affordable, and reducing the time from testing to result (Peeling and Olliaro, 2021; Peeling et al., 2021). A meta-analysis of studies on influenza diagnostic tests showed that in adults and children, both novel digital immunoassays and rapid nucleic acid amplification tests had substantially higher sensitivities for influenza A and B—with similarly high specificities—than traditional rapid influenza tests (Merckx et al., 2017). The correlation between the results for rapid influenza diagnostic tests and molecular tests for H1N1 influenza is relatively poor, but the Winthrop-University Hospital Infectious Disease Division's Diagnostic Swine Influenza Triad of nonspecific laboratory indicators can

be used to make a rapid clinical diagnosis in hospitalized, symptomatic patients with negative rapid test results (Cunha et al., 2010).

During the COVID-19 pandemic, testing asymptomatic individuals at high risk (e.g., residents of aged care or skilled nursing facilities, passengers on cruise ships, personnel on military ships) has had a high positive yield (Kasper et al., 2020; Kimball et al., 2020; Oran and Topol, 2020). Despite little evidence to support mass testing without risk-based targeting, testing in combination with tracing and travel-related quarantine can be effective. A probability model theorized that testing on both entry and exit from quarantine can reduce the duration of 14-day quarantine by 50 percent and yield the greatest reduction in post-quarantine transmission events (Wells et al., 2021). South Korea, China, and Singapore have used digital contact tracing to control the spread of COVID-19, although this strategy raises privacy concerns and can be hampered by technical issues (Lancet Digital Health, 2020).

A modeling study estimated the impact of school reopening under various testing and tracing scenarios in the United Kingdom in September 2020, finding that a comprehensive test-trace-isolate strategy would be needed to avoid a second wave of COVID-19 (Panovska-Griffiths et al., 2020). If schools reopened full time and 68 percent of contacts were traceable, avoiding the second wave would require testing an estimated 75 percent of symptomatic cases and isolating positive cases. If only 40 percent of contacts were traced, 87 percent of symptomatic cases would need to be isolated. The authors posit that without such widespread testing and contact tracing, school reopening coupled with relaxing the lockdown measures would likely engender a second wave with an R that exceeds 1. However, other modeling research suggests that test-trace-isolate strategies alone have been insufficient without complementary measures, such as distancing and improved hygiene (Contreras et al., 2021). Lastly, modeling has shown that 62 percent of simulated transmissions occur in the presymptomatic phase for SARS-CoV-2, compared to 10 percent for influenza (Goyal et al., 2021), suggesting that testing asymptomatic individuals may have less applicability to influenza.

Case Isolation and Quarantine

If implemented early, isolation and contact tracing can be effective in controlling the spread of COVID-19, although these strategies may be less effective for influenza given its shorter incubation period. A mathematical modeling study estimated that in most scenarios, the combination of highly effective case isolation and contact isolation (supported by contact tracing) is sufficient to bring a new outbreak of COVID-19 under control within 3 months (Hellewell et al., 2020). However, another study modeled

the impact of case isolation and contact tracing in combination with other measures and found that adding moderate physical distancing measures would be more likely to achieve control; otherwise, achieving an Rt less than 1 would require isolating and contact tracing for very high proportions of cases (Kucharski et al., 2020). The findings of a rapid review of 29 studies indicate that quarantine contributes importantly to reducing COVID-19 incidence and mortality when implemented alone but is even more effective in combination with other measures, such as school closures, travel restrictions, and physical distancing (Nussbaumer-Streit et al., 2020). However, quarantines are logistically difficult to impose and can have adverse mental and physical health effects on individuals required to isolate for extended periods.

A summary of the evidence of various governmental and public health measures explored in this chapter (see Table 3-3) and a list of potential research topics that need additional study in this area (see Box 3-3) are outlined below.

TABLE 3-3 Governmental and Public Health Measures: Evidence Supporting Efficacy/Effectiveness* in Reducing Transmission of Respiratory Viruses

Public Health Measures	Strength of Evidence	Effectiveness/ Efficacy	Summary of Evidence (with Citation)
School closures	Moderate	Low to moderate depending on the pathogen	• During the COVID-19 pandemic, sustained school closures were not as effective at preventing community spread as they are for influenza, as children drive influenza transmission more (Bin Nafisah et al., 2018; Jackson et al., 2013; Stebbins et al., 2010).
Lockdowns, curfews, and stay-at-home orders	Moderate	Moderate	• Evidence suggests lockdown and curfew measures may reduce incidence, transmission, and mortality rates for SARS-CoV-2 and influenza (Sullivan et al., 2020), although these have economic and other implications. ◦ Research suggests that shelter-in-place orders decreased COVID-19 spread 10-fold and that these orders combined with three other interventions (large social gathering bans, school closures, and entertainment venue, gym, bar, and restaurant dining area closures) decreased it 35-fold (Courtemanche et al., 2020).

TABLE 3-3 Continued

Public Health Measures	Strength of Evidence	Effectiveness/ Efficacy	Summary of Evidence (with Citation)
Venue closures (other than schools)	Moderate	Moderate to high	• Studies indicate that mask-off settings, such as restaurants, are associated with greater risk of transmission of COVID-19 (Guy et al., 2021b; Martin Sanchez et al., 2021) and that reduced mobility is strongly correlated with decreased case growth (Badr et al., 2020; Courtemanche et al., 2020).
Case isolation and quarantine	Moderate	Moderate to high, depending on the pathogen	• A rapid review of 29 studies indicates that quarantine is effective in reducing COVID-19 incidence and mortality when implemented alone and even more effective in combination with other measures (Nussbaumer-Streit et al., 2020). • Case isolation and quarantine for influenza, however, may be less effective given its shorter incubation period.
Mass testing	Low	Low to moderate, depending on the pathogen and patient symptoms	• Molecular tests can be effective diagnostics during a pandemic but depend on production and testing capacity, which was limited during COVID-19 even in high-income countries (Peeling and Olliaro, 2021; Peeling et al., 2021). • While little evidence exists to support mass testing without risk-based targeting, testing asymptomatic high-risk individuals had a high positive yield during the COVID-19 pandemic (Kasper et al., 2020; Kimball et al., 2020; Oran and Topol, 2020). • An RCT in which prospective attendees at a large indoor music event were randomized to attend the event or continue with their normal activities provides preliminary evidence that same-day screening with an antigen-detecting rapid diagnostic test, combined with face masks and active air ventilation, creates a safe environment with no need for physical distancing (Revollo et al., 2021). • However, only 10 percent of influenza transmission occurs in the presymptomatic phase, suggesting that testing asymptomatic individuals has less applicability to influenza (Goyal et al., 2021).

continued

TABLE 3-3 Continued

Public Health Measures	Strength of Evidence	Effectiveness/ Efficacy	Summary of Evidence (with Citation)
Travel restrictions (including border closures and testing and quarantining travelers)	Moderate to high	Moderate, depending on timing of implementation	• Evidence around the emergence of variants of SARS-CoV-2 appears to justify border restrictions to reduce virus spread but only before significant community transmission is established (Cumming, 2021; Mallapaty, 2020; Pham et al., 2021). • Modeling several strategies, researchers determined that testing all travelers on entry and isolating those testing positive for 14 days would reduce case importation by 91.7 percent compared to no testing but that if good testing practices are not feasible, quarantining all persons for 14 days after entry should produce similar results (91.2 percent reduction) (Dickens et al., 2020).

* "Efficacy" refers to data from RCTs; "effectiveness" refers to data from experimental or observational epidemiologic studies.

BOX 3-3
Examples of Research Topics Related to Non-Vaccine Control Measures for Government and Public Health Controls

- Examine the personal and economic disruptions caused by curfews and lockdowns.
- Explore the impact of reopening schools and concerns with disease transmission regarding multigenerational households.
- Understand the infectivity and transmission levels of the Delta variant among children.
- Explore the effectiveness of screening programs when income protection or a safety net is or is not included for various types of populations.

EVIDENCE FOR COMBINATIONS OF MEASURES

Evidence from a large-scale review and other sources suggests that combinations of non-vaccine control interventions are more effective in curbing the spread of infectious respiratory viruses than single interventions in isolation. Furthermore, U.S. CDC recommends a layered approach of deploying public health measures for different thresholds of community transmission (CDC, 2021a). A review that quantified the impact on the effective reproduction of COVID-19 of more than 6,000 non-vaccine control

interventions across 79 territories suggests that no single intervention alone can halt the spread of SARS-CoV-2; instead, an appropriate combination is needed. The authors identified several interventions that significantly contributed to reducing Rt to less than 1, including curfews, lockdowns, and closing or restricting settings where people gather in smaller or larger groups for extended periods (Haug et al., 2020). This has been underscored by other studies showing that non-vaccine control interventions (e.g., moderate physical distancing measures, self-isolation, contact tracing) need to be used in combination for maximal effectiveness (Kucharski et al., 2020). Similarly, a hospital in Australia reported that diagnoses of SARS-CoV-2 and other respiratory viruses plunged after travel bans in conjunction with physical distancing (Marriott et al., 2020). In Taiwan, infectious respiratory diseases declined by 50 percent during the early phases of the COVID-19 pandemic compared to historical data from past influenza seasons. This decline has been attributed to a combination of universal hygiene interventions (e.g., handwashing, cleaning high-touch surfaces, ensuring access to medical-use alcohol) and mass masking policies that were complemented by strategies to educate the public about masks, ensure access to masks, and strongly encourage mask wearing in public (Hsieh et al., 2020).

OVERARCHING EVIDENCE

Most non-vaccine interventions currently have limited, mixed, or low levels of RCT evidence (WHO, 2019), although many have non-RCT evidence. Evidence for many of these interventions is by necessity ecological or observational, as it would not be possible or ethical to test some of them (e.g., lockdown, border closure) by RCTs. Furthermore, the science required for understanding of human respiratory emissions is experimental and has generated a body of robust evidence that is not well captured by evidence-based medicine frameworks. Some such evidence for respiratory aerosols is rooted in basic physical principles, which are as predictable as the effect of gravity, and does not require validation by RCTs. Additionally, the scientific community has found great success with the scientific method and laboratory experimentation for certain fields with a notoriously low tolerance for error. This pandemic has highlighted the interdisciplinary nature of infectious disease outbreaks, so the available overarching evidence guiding policy decisions and recommended interventions should also reflect that multi-sectoral influence. However, current research funding and opportunities remain largely siloed and are limited to efforts within certain fields. Without more integration, progress in understanding the intersection of these critical fields might not occur. This type of detailed development and quality evaluation research must occur between pandemics, not once they have already begun.

Some relatively robust studies provide overarching evidence about the synergistic effects of certain combinations of non-vaccine control measures in curbing the spread of both COVID-19 and pandemic influenza. Using longitudinal regression, a review of the literature found strong evidence for an association between school closures, internal movement restrictions, and reduced Rt (Liu et al., 2021). Workplace closure, income support, and debt/contract relief had strong evidence of effectiveness if levels of intensity were not taken into account. Cancellations of public events and restrictions on gatherings had strong evidence of their effectiveness but only when implementation at maximum capacity was evaluated—for instance, restrictions were not effective for gatherings of greater than 1,000 people but were effective for less than 10 people. The focus of effectiveness in this chapter is measures' abilities to reduce virus transmission; the next chapter explores social, economic, and other contextual factors that can affect the implementation and overall population optimization of these measures.

A systematic review of pandemic influenza mitigation literature reported that vaccination appears to confer significant protection against infection but evidence was insufficient to identify appreciable protection from antiviral prophylaxis, seasonal influenza cross-protection, or various non-vaccine control interventions in isolation. The authors propose that an optimal strategy would likely feature a layered combination of interventions (Saunders-Hastings et al., 2016).

According to a modeling study based on daily data from 175 countries, public event cancellations, private-gathering restrictions, and school and workplace closures significantly reduced the number of COVID-19 infections, even after controlling for additional lockdown policies that were in place (Askitas et al., 2021). Restrictions on internal movement and public transport had no such effects—likely due to lockdown policies—while less-stringent restrictions on international travel imposed early in the pandemic had a short-lived effect.

CONCLUSIONS

Overarching

It is important to introduce public health interventions in combination as a layered preventive approach to maximize the reduction in the risk of transmission. A number of factors should be considered when determining the approach that is best for a particular setting to reduce harm to livelihoods, including the effectiveness of measures in reducing viral transmission as well as economic and other contextual factors.

There is a need for a research framework to address the gaps in evidence for particular public health interventions that takes into account

that the way evidence is best assessed for each measure may differ, since some interventions cannot be tested in a randomized controlled trial (RCT) that assesses measures in combination as well as separately and that tests mandates for influenza. This should consider that some science, such as aerosol and physical sciences and engineering, provides the best evidence for specific questions and that in some cases interventions (e.g., national border closure) cannot be tested in RCTs because doing so is not feasible or ethical, so that ecological or observational studies would be required. Better integrating research in these different fields can inform not only various methodologies but also more complete understanding of interventions and impacts.

Individual-Level Actions

Multiple lines of evidence show that face masks are effective in reducing COVID-19 transmission, and face masks should also be effective for influenza. For seasonal influenza, jurisdictions could consider a mandate depending on the setting and the incidence and severity of circulating strains. For example, masks could be mandated in hospitals during the influenza season. During a pandemic, appropriate types of masks and their use should be mandated, in part because they are less costly and less disruptive than other interventions and may avert the need for a costly lockdown. The best-performing masks consist of suitable materials with high filtration efficiency, fit well with no leaks, and have a low pressure drop for ease of extended use and breathability.

Face shields are intended to be worn over masks and are used in medical settings to avoid splatter. They do not reduce exposure to aerosols. They are not a substitute for masks in the community, businesses, mass gatherings, or modes of transportation, including cars, buses, trains, ships, and airplanes. Their effectiveness when used alone is limited at best.

Physical distancing measures, overall, have some evidence for effectiveness. Distancing of 1–2 m reduces but does not eliminate transmission. Factors such as airflow direction, duration of exposure, and use of masks and other interventions influence the efficacy of physical distancing.

Building and Environmental Controls

Among the types of building and environmental controls evaluated during COVID-19 that may have applicability for influenza, ventilation/filtration systems have the most evidence of demonstrated effectiveness in reducing virus transmission. The World Health Organization and professional organizations need to develop evidence-based guidelines for ventila-

tion and filtration during a pandemic, and the relevant authorities in each country around the world need to incorporate these into their building standards. Short-term mitigation measures, such as air purifiers and information on proper use to avoid negative airflow patterns, should also be made available.

Transparent barriers alone are effective only in the specific scenario of a brief, face-to-face interaction involving two people; in fact, barriers may be harmful because they can create "hot spots" where particles accumulate and impede proper ventilation in a room. Masks are preferred because they remove particles, whereas barriers simply divert them.

Government and Public Health Controls

Studies during the COVID-19 pandemic produced evidence that highly restrictive, mandated measures, such as curfews and lockdowns, were effective in reducing virus transmission. They can be expected to produce similar results for influenza, but any decision to impose such measures would need to take into account their disruptive effects on personal life and the economy during the current pandemic.

Since the SARS-CoV-2 virus had been spread by travelers to a number of countries before the World Health Organization recognized the novel coronavirus as a Public Health Emergency of International Concern—and even more so, before it declared COVID-19 a pandemic—there is little evidence that the restrictions on cross-border travel that many countries imposed were effective in reducing viral transmission during COVID-19, as is likely to be true in an influenza pandemic as well. Nonetheless, border closures—for example, by island nations—can be effective when imposed before community transmission is established, provided that any persons allowed to enter are quarantined, as should be true for all entrants who have recently been in countries where the virus is known to be present.

There is some evidence during COVID-19 that children are not the main drivers of SARS-CoV-2 transmission, unlike influenza, where children play a major role in transmissibility in the community because they shed virus for longer and at higher levels. Hence, school closures may be more effective during an influenza pandemic at reducing virus transmission compared with during COVID-19; however, given the continued emergence of COVID-19 variants, such as Delta, vigilance in monitoring the transmissibility among children is needed.

Evidence from the COVID-19 pandemic suggests that closing indoor venues, such as restaurants and churches, where people do not wear masks all the time (i.e., while eating, drinking, singing) may reduce virus transmission, but the emergence of recent variants of concern may influence the effectiveness of this intervention.

For mask mandates to be effective, public health agencies need to communicate clearly with the public about the value of particular types of masks, how to use them correctly, and when and where they should be worn.

The combination of testing, case isolation, and contact tracing has documented effectiveness for reducing transmission of COVID-19, especially when implemented early, but this strategy may be less effective for influenza due to its short incubation period. Although the evidence is incomplete, mass testing that is not targeted to groups at highest risk has not been shown to be effective in reducing viral transmission.

RECOMMENDATIONS

Recommendation 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.

Recommendation 3-2: Global, state, and local public health agencies and other entities should mandate wearing face masks that comply with the World Health Organization's guidance, when justified by the incidence and severity of influenza.

Recommendation 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.

Recommendation 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.

Recommendation 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.

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4

Implementation of Non-Vaccine Control Measures

The coronavirus disease 2019 (COVID-19) pandemic has starkly illustrated the extent to which countries were underprepared to respond to a major pandemic, fostering an environment in which interventions to prevent and mitigate transmission of a viral respiratory pathogen were likely to fail from the outset. Interventions during the response to the pandemic could have been informed and strengthened by many lessons learned during the responses to previous epidemic and pandemic events, such as the Ebola virus disease outbreaks in sub-Saharan Africa (SSA) (2014–2016) and the global H1N1 influenza virus pandemic (2009). However, largely due to lack of funding, many of the gaps identified in those responses were never rectified (Afolabi et al., 2021). Additionally, for reasons unknown, many of the lessons learned during those epidemics were not translated into improvements in the COVID-19 responses. For example, the Ebola outbreaks highlighted the critical need for community engagement, clear and coordinated risk communications, and avoidance of contradictory messaging. But while countless reports were written about these experiences in the years following, those approaches were not immediately used when the COVID-19 pandemic began. Insufficient resources for public health systems persists as an ongoing issue that undermines countries' preparedness and response capacities related to infectious disease threats (Edelman et al., 2020). Moreover, the limited international cooperation in responding to the pandemic—including the announcement in May 2020 that the United States would withdraw from the World Health Organization (WHO) (which was rescinded in 2021)—weakened the response efforts in countries and fractured the landscape of global diplomacy (Gostin et al., 2020). Drawing

on lessons learned during the pandemic, this chapter focuses on strategies for effectively implementing non-vaccine control measures by exploring (1) how community-specific social and cultural factors can aid or hinder implementation, (2) how evidence-based communication strategies can promote population uptake of recommended measures, and (3) how a rapid, coordinated government response bolstered by strong and consistent leadership can catalyze a positive response to public health interventions.

CONTEXTUAL FACTORS AFFECTING IMPLEMENTATION

A host of social, cultural, and structural factors influenced the public's reception and uptake of non-vaccine control measures during the COVID-19 pandemic. Understanding the interplay between these factors will help to inform more effective strategies for designing community-specific interventions that garner greater public support and higher rates of adherence during future outbreaks (see Box 4-1).

Sociocultural Factors

Public responses to non-vaccine interventions are profoundly shaped by a range of social and cultural values, beliefs, and norms that vary across communities around the world. A rapid systematic review of community-based interventions and practices during COVID-19 and previous outbreaks of respiratory infections implemented in low- and middle-income countries (LMICs) found that masks, hand hygiene, and physical distancing

BOX 4-1
Examples of Research Topics Related to Contextual Factors Affecting Implementation

- Tracking racial, ethnic, socioeconomic and similar data systematically during an outbreak.
- Examining how the timing, duration, and intensity of interventions influence population uptake in various settings.
- Exploring the influence of a community's religious practices and institutions on its response to an epidemic and adherence to public health interventions.
- Exploring the impacts of historical trauma experienced by certain populations and how it affects their trust in government bodies and corresponding mandates or recommendations.
- Analyzing ways of implementing public health interventions that do not stigmatize those with the disease.

were effective in reducing virus transmission in the community. However, their overall effectiveness depended on people adhering to the interventions in different contexts; adherence is shaped by social norms and beliefs and economic and logistical factors. Understanding community-specific socio-cultural practices is thus critical in designing strategies and best practices to promote adherence, such as tailored communication to encourage behavior change (Abdullahi et al., 2020).

An important aspect of a community's values is the degree to which its members conceive of themselves as primarily either independent or interdependent beings. For instance, individualism and independence are highly valued in many cultures in Europe and North America. In contrast, cultures in Asian countries tend to be more interdependent, place higher value on community well-being, and prioritize adherence to social norms over personal desires (Van Bavel et al., 2020). Differences in high-income countries' uptake of interventions during the pandemic evidenced the influence of cultural variations of this sort. For example, in Japan, individuals are more likely to follow government advice for the benefit of the entire community, while in the United States, many people have deeply held libertarian values that prioritize personal liberties and are more prone to disregard government advice (Reich, 2020).

Regional location, level of education, and beliefs about science have also affected how individuals have responded to interventions during the pandemic. A cross-sectional study was conducted in China to investigate differences in how residents of urban and rural areas responded to interventions that were intended to encourage behaviors to prevent transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Chen and Chen, 2020). Compared to urban populations, residents of rural areas were less likely to adopt preventive measures; they were also less likely to engage in the process of information appraisal[1] in considering whether to do so. A study in the United States that used cell-phone location data to gauge adherence to physical distancing directives demonstrated the influence of belief in science on the adoption of COVID-19-containment measures; the researchers found that the proportion of people adhering to lockdown policies was significantly lower in areas with large proportions of climate change skeptics (Brzezinski et al., 2020).

A community's behavior is also affected by various practical considerations and expectations related to employment, school attendance, and other activities that are typically conducted in person. A review of the implementation of personal actions, such as physical distancing, that were recommended to mitigate the transmission of SARS-CoV-2 found

[1] Information appraisal skills involve critical thinking and considering the application of health information to one's own life.

that their effectiveness is largely contingent upon the specific culture and context. For example, in SSA, the applicability of and compliance with interventions used in other parts of the world would largely depend on the resources available and the timing, duration, and intensity of each intervention (Amaechi et al., 2020). This was also the case in Latin America, where an important proportion of the population, which had informal employment with precarious income, was not able to follow stay-at-home orders or isolation without income support (Garcia et al., 2020).

A community's religious and family values can also impact health-related behaviors and undermine adherence to non-vaccine control interventions. In Malaysia, cases of COVID-19 spiked after a series of large religious gatherings that were attended by thousands of people (Tan et al., 2021). Although religious leaders may advise congregants to practice physical distancing in other contexts during an outbreak, many individuals believe they enjoy divine protection while attending religious ceremonies. In many communities around the world, religion serves as the foundation and structure for virtually all dimensions of social life and shapes a broad range of private and public behaviors—including those related to the mitigation of infectious disease (Baker, M. G. et al., 2020).

Early in March 2020, a Modern Orthodox Jewish community whose members reside in several New York City boroughs and beyond became the first community in the United States to be quarantined, based on the group's tight-knit religious and educational institutions rather than geographic proximity. The group's strong communal links likely contributed to it becoming one of the most heavily impacted, first by the disease itself and then by the adverse psychosocial effects of interventions intended to mitigate the pandemic. For example, community members experienced elevated levels of stress, anxiety, and perceived stigma directly associated with the lack of consistent communication from local public health departments (Weinberger-Litman et al., 2020). More research is warranted to inform decisions about which types of interventions should be implemented during future outbreak events and diminish their potential adverse consequences. This research could focus on the interplay between epidemics and religious groups and their gatherings and the positive and negative influences of religion on a community's response to an epidemic and adherence to public health interventions.

Social and Structural Determinants of Health

Along with social and cultural values, strategies for successful implementation of non-vaccine control interventions should take into account the critical variables of community-specific social and structural determinants

of health, including disparate treatment of certain racial and ethnic groups and socioeconomic inequalities.

Racial and Ethnic Disparities

It is now well established that racial and ethnic disparities underlie a range of barriers to accessing quality health care (NASEM, 2017). In all countries, the COVID-19 pandemic has made tragically apparent the existing inequities in access to resources and long-standing biases and prejudices that have long undermined the health of affected populations. The pandemic has also exacerbated the confluence of factors driving health inequities that some communities—typically defined by race, ethnicity, and socioeconomic status—have experienced for generations. During the pandemic, this confluence of factors driving health inequities has heightened the risk of exposure to the virus due to occupational or living conditions and led to greater prevalence of noncommunicable diseases that increases the rates of severe disease and mortality due to COVID-19 in adversely affected groups (Maani et al., 2021).

In the United States, historically marginalized racial and ethnic groups—including Black, Hispanic, Asian, American Indian, and Alaska Native populations—have been disproportionately impacted. Although many jurisdictions failed to report racial and ethnic data early in the pandemic, by July 2020, researchers had documented this disproportionate impact—as seen in disparities in testing, infection rates, and outcomes, including hospitalization and death—in the nonwhite population. In the United States, the highest COVID-19-related fatality rates were among racial and ethnic minorities (CDC, 2021), even in states where racial and ethnic minorities only make up small percentages of the total population (KFF, 2021). An analysis of U.S. patient health record data found that hospitalization rates and death rates per 10,000 were substantially higher for Black (24.6 and 5.6, respectively), Hispanic (30.4 and 5.6), and Asian (15.9 and 4.3) people than for white people (7.4 and 2.3) (Lopez et al., 2021).

Similar results exist on a global level among migrant and ethnic minority groups, who experienced higher COVID-19 infection rates and disease severity (UN News, 2020). The United Kingdom, Sweden, Brazil, Spain, and South Africa have all reported higher rates of severe disease and death among those groups, who also tend to have limited access to testing and poor outcomes after recovering from the infection (Melchior et al., 2021). Despite these well-established disparities related to COVID-19, most countries—even those with large immigrant populations—do not report their statistics by ethnicity or migrant status, highlighting the importance of research to develop systems for tracking such data during an outbreak.

Socioeconomic Inequalities

Socioeconomic inequalities can severely impact health outcomes during an outbreak, which underscores the need for national and international efforts to prioritize vulnerable groups in response to a pandemic. For example, in Brazil, communities and individuals from socioeconomic and ethnic groups that suffer from inequality had less capacity to prevent and recover from COVID-19 infections (Tavares and Betti, 2021). A population-based seroepidemiological study conducted in Lima, Peru, demonstrated that both lower socioeconomic status and overcrowding in households were linked with greater SARS-CoV-2 seroprevalence (Reyes-Vega et al., 2021). Similarly, an analysis that compared COVID-19 disease incidence and mortality in high- and low-income municipalities in Santiago, Chile, reported a strong association between socioeconomic status and COVID-19 outcomes, with a greater infection fatality rate among younger people living in lower-income municipalities (Mena et al., 2021). Furthermore, they found that people living in lower-income areas did not adhere to lockdown orders as stringently as those in higher-income areas.

Housing conditions and location, and household composition can also intensify or ameliorate risks along socioeconomic lines during a viral respiratory outbreak. Across the world, an estimated 1 billion people live in high-density communities and informal settlements with overcrowded dwellings and poor sanitation—often referred to as "slums"—that intensify their existing vulnerabilities during outbreaks of infectious diseases (Friesen and Pelz, 2020). The COVID-19 pandemic has exposed the lack of robust data on the people in such communities, their health statuses, and their living conditions—all of which limit the effectiveness of non-vaccine interventions for infection prevention and control (Wamoyi et al., 2021).

Moreover, people living in slum communities and crowded homes are less likely to have access to basic preventive measures, such as handwashing (World Bank, 2020b) or space where sick residents can be isolated. In Latin America, residents of these settlements also struggle with improved housing due to a "lack of land availability, affordable construction materials, infrastructure connections, access to urban amenities" (McTarnaghan et al., 2016, p. viii). Many townships in South Africa lack running water in homes, with many residents living in close quarters (Trenchard, 2020). Growing urbanization in countries such as Kenya, Tanzania, and Uganda and increases the number of people per household; it is estimated that in 57 percent of urban households, residents share a single room and thus are unable to practice physical distancing and other prevention measures implemented in other countries (Lirri, 2020; Wayomi et al., 2021).

The ability to comply with stay-at-home orders is likewise affected by income and occupation. Many wage-earners who work in the informal

sector may not be able to comply with stay-at-home orders due to needing to provide for their families (Wamoyi et al., 2021). Data aggregated from 40 million mobile devices at the county level in the United States showed that households with higher incomes adhered more closely to stay-at-home orders during the COVID-19 pandemic, as evidenced by less mobility outside the home, than did lower-income households. This could be attributed in part to broader options for working remotely compared to households whose income depends on jobs involving direct, in-person labor (Singh et al., 2021).

Workarounds to Unchanging Social and Structural Factors

While identifying the social and structural determinants of health is important, these often will not be resolved quickly, so many typical interventions may not be effective for certain populations or in certain locations. Policy consideration of these factors is necessary, but so is creative research and documentation of best practices to have a more comprehensive understanding of what non-vaccine measures can be reasonably implemented in difficult settings (i.e., in urban slums where quarantine of infected family members is not feasible or in schools with outdated or poorly functioning heating, ventilation, and air conditioning systems) to provide some level of protection. Locations where many in the population face these challenging factors and do not have equitable access to effective vaccines have had to depend on creative workarounds throughout the COVID-19 pandemic. For example, despite predictions that African health systems would be quickly overwhelmed when the outbreak spread, most countries have still reported relatively few cases compared to much wealthier and more industrialized countries. Binagwaho and colleagues (2020) outlined seven contextual factors as key facilitators or barriers to implementation of interventions: culture of accountability, national coordination, financial stability of the population, culture of innovation, culture and capacity of research, strength of the health sector, and cross-border economies. They also suggested potential strategies to address the factors, such as task shifting from clinicians to community health workers and community-based engagement to lessen the burden on the health sector. Numerous innovations developed in Africa, such as low-cost rapid test kits or locally manufactured ventilators, can be leveraged by putting them in the hands of the right workforce.

Other workarounds to these structural and social factors may include encouraging mask wearing in every setting that lacks access to vaccines, conducting classes outside, or alternating which groups of students attend school in person on different days. However, it is unclear whether any of these are effective or whether and when they outweigh the societal burden. More research is needed on the ad hoc interventions to reduce the spread in

different countries, as this is an opportunity to learn more about which were effective or ineffective. These interventions should also be conducted within a framework of implementation research, allowing for adapting and improving the practices and informing future work examining real-world effectiveness.

COMMUNICATION APPROACHES TO PROMOTE UPTAKE

The methods by which evidence, policies, mandates, and other information related to COVID-19 are communicated significantly impact the public's perceptions and uptake of public health interventions intended to prevent and mitigate transmission. Health care professionals have found that public communication strategies should be clear, credible, and consistent to promote compliance with recommended interventions (Hung and Lin, 2021). Science communication, "the art and technique of informing, influencing, and motivating individual, institutional, and public audiences about important health issues" (HHS, 2000), is critical to conveying how new research informs policy and individual behavior (Goldstein et al., 2020). However, recommendations inevitably may have to be revised based on research, which occurred frequently and rapidly with COVID-19 (Fraser et al., 2021). Thus, the public needs timely reminders that guidance and mandates may change to stay consistent with the best current evidence rather than being constant over time. Additionally, officials need to gather—and use—data on the public's understanding of, and adherence to, public health guidance in order to formulate public health policies and communication strategies that will increase the uptake of non-vaccine control interventions (Timmons et al., 2021). Additional research to inform communication approaches are outlined at the end of this section in Box 4-2.

BOX 4-2
Examples of Research and Programmatic Opportunities for Communication Approaches

- Analyzing the positive and negative impacts of using mass media as a platform for public health communication.
- Gathering data on the public's understanding of, and adherence to, public health guidance to formulate public health policies and communication strategies.
- Leveraging ways that community engagement can be most fully used to implement public health interventions during a pandemic.
- Exploring the impact of the new communication modalities developed during the COVID-19 pandemic, with attention to inequalities in access to such modalities.

Factors Impacting Public Perceptions and Compliance with Interventions

Many modes of communication can be used to disseminate public health information to the public, which will have different effects on the responses of different groups. Receptivity to non-vaccine infection control measures is influenced by individual psychology and a range of sociodemographic factors, such as age and gender. For example, warning is a key component of crisis communication, which focuses on rapidly providing the public with information about impending or ongoing hazards and how to respond to them (Rahn et al., 2021). A cross-sectional survey in Germany on compliance with warnings during the COVID-19 pandemic found that older adults were more likely to comply (Rahn et al., 2021). In another study of perceptions and behaviors related to COVID-19 public health measures in Canada, men, people in younger age groups, and members of the paid workforce were less likely to report that they considered the measures to be effective and less confident in their ability to comply (Brankston et al., 2021).

Other factors that impact compliance include communication style and the perceived psychological distance between the audience and the communicator. Psychological distance is a multidimensional construct spanning four types of distance: spatial (i.e., physical proximity), social (i.e., friend versus stranger), temporal (i.e., now versus next year), and hypothetical (i.e., high-probability versus low-probability event). A multi-site study in the United States looked at the impact of perceived distance on the effects of an aggressive public communication style used to convey scientific information about COVID-19 (Chu et al., 2021). The use of aggressive language and tactics, including name-calling or other personal attacks, was found to increase compliance if the recipients perceived the communicator as psychologically close to them. This suggests—somewhat counterintuitively—that aggressive communication can strengthen public health strategies if the communicator has developed a close connection with the audience. Furthermore, the framing of public health communication can influence compliance with measures, including use of "positive" communication and language or tone (Biroli et al., 2020; McGuire et al., 2020). For example, one study found that communication focused on individual victims of the pandemic had a more positive impact on compliance than communication about statistical cases, as is common in "flatten-the-curve" campaigns (Byrd and Białek, 2021).

These findings suggest that the most effective strategies and channels of communication about public health measures vary according to a range of factors. Tailoring communication to specific sociodemographic groups could help bolster acceptance of, confidence in, and adherence to interventions in an outbreak context. For instance, communication about risks and

disease outcomes that is intended to engage young adults and dispel myths and misinformation might be most effectively delivered using technologies and social media platforms that they favor (Hung and Lin, 2021). Communication about interventions should also be tailored to specific cultures and settings to effectively engage different segments of the public. Public strategies during the COVID-19 pandemic have tended to focus on individual risks rather than the community risks that are the consequence of existing inequities (Airhihenbuwa et al., 2020). Communication about physical or social distancing may impart differences in cultural contexts where communities are more collectivist than individualist, for example. Lastly, social and societal values and the population's trust in leadership and science, as discussed later in this chapter, can greatly impact uptake of preventive public health measures.

Understanding Public Perceptions of Interventions

A wealth of data is available from online sources that could be leveraged to better understand the public's perceptions about interventions in order to inform and refine communication strategies. For example, evidence suggests that perception of non-vaccine interventions is largely dependent on their restrictiveness. Social media platforms can provide sources of timely data and feedback about the public's responses to such interventions (Doogan et al., 2020). A topic modeling analysis of Twitter posts in six countries (Australia, Canada, Ireland, New Zealand, the United Kingdom, and the United States) looked at public perceptions of interventions such as masks and physical distancing. The study found that less restrictive measures garnered more widespread support and that more restrictive measures were perceived in different ways across those countries. Four characteristics were identified as influencing public adherence to the interventions: (1) timely implementation, (2) style of campaign strategies, (3) prevalence of inconsistent information, and (4) use of enforcement strategies (Doogan et al., 2020). A qualitative assessment of social media posts in South Africa during the COVID-19 pandemic revealed that false information circulated on social media can have multiple effects. In addition to instigating fear, confusion, and panic, it contributed to othering and stigmatizing responses and misconceptions that could potentially be mitigated by community-specific strategies (Schmidt et al., 2021).

Mass media have a substantial influence on the public's knowledge about viral respiratory pathogens and their associated risks. This was demonstrated during the COVID-19 pandemic and other coronavirus outbreaks when inconsistencies in the public's understanding of these pathogens affected the public's response, level of concern, and uptake of preventive interventions (Yu et al., 2021). Additionally, the constant barrage of infor-

mation led to what WHO called the "infodemic," or an overabundance of information online and offline that sometimes included deliberate efforts to spread disinformation (WHO, 2021b). This has been exacerbated through social media, negatively influencing many around the world and affecting public health knowledge and response. Although media bias in various countries may have had deleterious effects on intervention uptake, the media can also be leveraged positively. A community-based study of knowledge, attitudes, and practices toward COVID-19 in Southern Ethiopia found that media campaigns can promote knowledge, awareness, and uptake of preventive measures in rural areas (Yoseph et al., 2021). Search engine data can also offer rapid and location-specific information about the impact and perception of public health strategies and potentially conflicting communication being delivered via mass media. An analysis of the timing and relative volumes of search engine terms related to COVID-19 in Germany found that most searches for "protective masks" occurred early in the country's first wave—a period with conflicting recommendations about whether to wear face masks—suggesting that the phrase had created a degree of confusion among the population (Kristensen et al., 2021). More positive examples of how to leverage tools such as social media to optimally benefit public health are needed.

Developing Community-Focused Communication Strategies

The community should play an active—rather than passive—role in the response to an infectious disease outbreak or other public health emergency. Developing community-focused communication strategies can help foster community engagement and encourage adherence to non-vaccine control interventions. WHO defines community engagement in the context of health as "a process of developing relationships that enable people of a community and organizations to work together to address health-related issues and promote well-being to achieve positive health impact and outcomes" (WHO, 2020). However, engaging communities in this type of active participation during lockdowns or when large gatherings are limited creates major challenges. For these efforts to be successful, much of the outreach and relationship building needs to be done before an outbreak begins. For the times that soliciting community input in real time is necessary, creative approaches on how to facilitate that participation should be developed beforehand as well, so they can quickly be put into practice when needed.

Developing a bottom-up, community-specific communication strategy—for example, by eliminating language barriers and involving local leaders—during a public health crisis can help to build public trust and contribute to the success of prevention and response efforts. This was

demonstrated by the effectiveness of a community-adapted communication strategy implemented in Orthodox Jewish communities in Belgium during the first COVID-19 lockdown; however, stigmatization can be a potential drawback of this approach (Vanhamel et al., 2021). Although community engagement through bottom-up approaches is critical during an epidemic, and such approaches were robust during previous outbreaks, such as Ebola (2014–2016), they have not been fully optimized during the COVID-19 pandemic. A rapid review of evidence examined the use of community engagement in infection prevention and control during past epidemics, identifying five key functions: (1) entering communities and building trust, (2) communicating to drive social and behavior change, (3) communicating risks, (4) conducting surveillance and contact tracing, and (5) providing logistical and administrative support (Gilmore et al., 2020).

A mixed approach to communication with the public may be the most effective in many contexts. In Malaysia, public communications by the Ministry of Health during the COVID-19 pandemic was divided by subject categories, including disease information, state-mandated lockdowns, prevention, reference information, standard operating procedures, and other key information. It developed infographics in languages spoken by the local population that were intended to raise awareness, change and challenge attitudes, and present a call to action for the public to adopt healthy behaviors (Jerome et al., 2021). Similarly, to help reach vulnerable local populations, community-engaged research partnerships in southeast Minnesota translated COVID-19-related communication into six languages; community leaders used multiple electronic platforms and networks to deliver the communication (Wieland et al., 2020).

Community and opinion leaders (including "social influencers") can affect public perception during a health emergency (Quinn, 2020). Specific communities with a history of medical mistrust have previously used members and leaders of those communities to improve community engagement with public health strategies, such as with HIV/AIDS testing and prevention in the United States (Kalichman et al., 2016; Li et al., 2013). Religious leaders can also have positive and negative effects on the community. In Nigeria, a small qualitative survey found that people were more likely to follow handwashing and mask-wearing strategies during COVID-19 if the information came from a church or religious leader (Nnama-Okechukwu et al., 2020). On the other hand, some religious leaders and communities were committed to maintaining pre-COVID-19 practices and actively worked against public health prevention efforts (Levin, 2020) or aligned with government leaders whose partisan politics were openly hostile to public health efforts, such as in Brazil (Bandeira and Carranza, 2020).

Research Gaps Related to Communication Approaches

During the COVID-19 pandemic, many people relied on digital communication as their exclusive means of social connection for lengthy periods, leading to changes in the patterns of how people use these digital channels—shaped by various demographic and socioeconomic factors—that will likely persist after the pandemic is over (Nguyen et al., 2020). Although digital communication has provided a valuable outlet for many people, access is unequally distributed across the world, contributing to the infodemic that has resulted in confusion among populations and growing distrust toward official sources of information. The post-pandemic impact of new communication modalities and patterns on such inequalities warrants further research. One of the challenges throughout the pandemic has been trying to ensure coherent communication of public health and scientific knowledge in an environment where new information and research rapidly emerges. In some cases, the new information may conflict with the previous findings and guidance, challenging the public's trust, but clear methods for communicating this have not been identified. Also lacking in research are the positive and negative impacts of using mass media as a platform for public health communications (Anwar et al., 2020). Such research could inform strategies to effectively communicate reliable health information and health education despite the large volume of parallel information—some of which may be false and/or unsourced—being delivered through social and mass media (Mheidly and Fares, 2020).

GOVERNMENT RESPONSE AND LEADERSHIP TO SUPPORT IMPLEMENTATION

Governments are the primary actors in determining how non-vaccine interventions are created, communicated, and deployed in the context of an epidemic or pandemic. Although the committee took into account social contexts, communication methods, and other factors that influence the implementation and uptake of such interventions, their effectiveness is ultimately contingent upon coordination that is spearheaded by strong leadership and governance. More research in this area could inform types of interventions, and examples of topics are listed in Box 4-3.

Rapid and Coordinated Government Action

Many lessons gleaned from effective pandemic response efforts around the world highlight the importance of swift, proactive government action and effective coordination within and across sectors. A well-coordinated, multi-sectoral response is key to success so that the epidemic or pandemic

BOX 4-3
Examples of Research Topics Regarding Leadership and Governmental Response

- Studying the potential long-term economic impact of restrictive public health interventions on various industries.
- Determining the mix of mandated versus voluntary policies that most effectively optimizes the population's uptake of interventions.
- Developing knowledge about the effective implementation of policies by including this topic in major research agendas for respiratory viruses.
- Discovering how to rapidly create, and sustainably implement, evidence-based public health policy in a pandemic.
- Determining how governments can best communicate changes to policy and mandates as the available evidence evolves.

is not seen and managed as simply a health issue. Both WHO's Independent Panel for Pandemic Preparedness and Response and the Lancet COVID-19 Commission Task Force for Public Health Measures to Suppress the Pandemic found that in successful countries, governments acted early and were proactive, whereas those that were unsuccessful were delayed in their response or denied the severity of COVID-19 (Lee et al., 2021; Sirleaf and Clark, 2021). For instance, a critical component of New Zealand's success in eliminating transmission nationwide was rapid, science-based risk assessment linked to early, decisive government action (Baker, J. O. et al., 2020). The Lancet COVID-19 Commission Task Force reported that countries where partnerships were forged across sectors and at various levels performed well, because communication was transparent and consistent (Sirleaf and Clark, 2021). Furthermore, the strength of the public health enterprise, both day to day and in times of crisis, depends on nonpartisan support. Political partisanship can—and does—undermine efforts to operationalize scientific knowledge by implementing evidence-based interventions (Narayan et al., 2021). Weak political coordination, anti-science sentiments, and distrust of political leaders have also been documented as adversely impacting the uptake of non-vaccine control measures during the pandemic (Anttiroiko, 2021; Desson et al., 2020; Feachem et al., 2021; Ferigato et al., 2020; Lancet, 2020; Migone, 2020).

Leadership and Trust

With country governments at the forefront of the COVID-19 response—and varying reactions to the pandemic by leaders within both political and

public health institutions—decisive leadership has emerged as a key factor in determining the success of non-vaccine control interventions. Unfortunately, several countries were also influenced by political campaigns or other political tensions, leading to noncompliance or failure to implement recommended health measures. As the Delta variant continues to surge in the United States at the time of this report, these challenges are still seen, with various state governors going against public health recommendations in hopes of garnering more support from constituents.

The successful responses to the COVID-19 health crisis enacted in New Zealand, South Korea, and Vietnam have been attributed, in part, to their leadership (Bhalla, 2021). For instance, empathic leadership in New Zealand effectively used the rallying cry that combating the pandemic was the work of a unified "team of 5 million." A high degree of public confidence and trust[2] contributed substantially to high levels of adherence to a suite of relatively burdensome pandemic-control measures (Baker, M. G. et al., 2020). This resulted in overwhelmingly positive outcomes: by mid-June 2021, New Zealand had reported only 26 deaths (WHO, 2021a). In contrast, adherence to quarantine orders in Colombia was undermined by poor coordination between the national government and the mayors and governors at regional and local levels. This gave rise to political tensions at the government level, confusion among the population, and public resistance to curfews across the country (Garcia et al., 2020). Effective national responses facilitated by strong leadership, such as New Zealand's, illustrate the importance of several key factors, including the rapidity of response, good coordination, an evidence-based approach that is communicated effectively, and the partnership spirit (Al Saidi et al., 2020; Lee et al., 2021).

In addition to strong leadership, building public trust is crucial to ensuring compliance with non-vaccine control interventions. A survey conducted in 11 countries evaluated public perceptions of more than 40 different containment measures. Researchers found significant variations in perceived effectiveness, restrictiveness, and compliance (Georgieva et al., 2021). Such findings suggest that in environments with low levels of public trust in government, compliance can be improved by offering incentives, such as supplements for people who have lost their jobs. No single crisis communication strategy is appropriate for all contexts, but an analysis of government approaches during COVID-19 found that the most effective strategies for developing and maintaining public trust are bidirectional,

[2] "In its broadest sense, political trust refers to citizens' assessments of the core institutions of the polity and the most relevant attributes that make each political institution trustworthy, such as credibility, fairness, competence, transparency in its policy-making, and openness to competing views" (Zmerli, 2014).

clear, tailored for diverse audiences, and delivered using appropriate platforms by trusted actors (Hyland-Wood et al., 2021).

Trust as a component of the relationship between the population and its leadership is predicated on shared values and, in several countries, shared values along political divisions can undermine attempts at unified communication from scientists and leadership. An example is using public health measures that require physical distancing despite adverse impacts on the local retail economy (Evans and Hagittai, 2020; Pagliaro et al., 2021). A low level of public trust in a country's government does not necessarily mean the population does not understand the scientific rationale or agree with countermeasures, as was found in Liberia during the Ebola outbreak (Blair et al., 2017). Additionally, a high level of public trust in a government does not always signal a high level of trust in science (Evans and Hagittai, 2020). This is further complicated when country leaders themselves do not comply with countermeasures, are openly hostile toward experts (Idrovo et al., 2021), or publicly display behavior that flouts public health mandates, such as not wearing masks in public or hosting large events that go beyond local mandates for physical distancing or limiting the capacity of venues (Lancet, 2020). Any scientific uncertainty—such as in the case of modeling mortality projections—can be politicized, which is particularly harmful in countries where partisan leadership is likely to promote information that lacks evidence (Kreps and Kriner, 2020). In a cross-sectional study of people in 23 countries, researchers found moral values can positively affect trust in government but negatively affect trust in science (Pagliaro et al., 2021).

Building trust is also a critical tool for counteracting misinformation, which abounds worldwide about the origin and response to the COVID-19 pandemic. A qualitative study of social media posts in Iran related to COVID-19 identified several factors that contributed to the spread of misinformation: (1) cultural factors, (2) demand for information during the crisis, (3) the ease of disseminating information through social media networks, (4) marketing incentives, and (5) poor regulation and legal review of online content (Bastani and Bahrami, 2020). An online survey looked at participants' evaluations of the believability of several COVID-19 narratives, finding that simply disseminating scientifically sound narratives may not be able to attenuate the public's beliefs in misinformation (Agley and Xiao, 2021). A more effective response to the proliferation of misinformation could involve strategies to foster the public's understanding and trust in science, scientists, and the scientific process.

Policy Considerations

In implementing stringent public health measures, a critical consideration for policy makers is how to strike the appropriate balance between

voluntary and mandated compliance by the public. Relying too heavily on the latter can undercut public support for measures and reduce public motivation to comply voluntarily (Schmelz, 2021). A survey conducted during the first COVID-19 lockdown in Germany found that a large proportion of respondents would be more likely to support voluntary measures (Schmelz, 2021). It has been suggested that at the outset of an outbreak, the least restrictive and most effective public health measures should be implemented first, rather than restrictive measures that have an adverse effect on adherence and can undermine human rights (Georgieva et al., 2021).

Prolonged, restrictive interventions to control disease outcomes have economic and social sequelae, such as increased unemployment and business bankruptcies (Chen and Qiu, 2020; Garcia et al., 2020). Individuals worried about losing income, for example, may be reluctant to comply with public health interventions, such as quarantining at home. A cross-sectional survey in Iran explored reasons for noncompliance with home quarantine during COVID-19; among the most frequently expressed were concerns about people's livelihoods and lack of government planning to support low-income groups (Nazari et al., 2020). Governments can help by assuring their citizens that livelihoods will be maintained during periods of restrictive measures. A cross-sectional study in Israel found that if respondents assumed they would be compensated for lost wages, compliance was 94 percent, but it decreased to 57 percent when compensation was removed (Bodas and Peleg, 2020). More research is needed on the potential long-term economic impacts of restrictive public health interventions on various industries. Additionally, regulatory governance strategies would benefit from integrating behavioral insights into a holistic outbreak response (OECD Policy Responses to Coronavirus, 2020).

Behavior Change Strategies

Governments and leadership should draw on experiences during the COVID-19 pandemic to inform the development and implementation of more effective behavior change strategies for use during future viral respiratory pathogen outbreaks. Containment strategies and mitigation strategies are two routes for changing individual and collective behaviors in response to an outbreak in the absence of an effective treatment or vaccine. Containment aims to reduce transmission by employing approaches such as early case detection, contact tracing, and confinement. Mitigation is intended to slow the spread and reduce the burden of demand on strained health care systems through measures such as physical distancing, lockdowns, and improved hygiene (OECD Policy Responses to Coronavirus, 2020).

Evidence gathered during the COVID-19 pandemic should be used to inform the development of effective behavior change strategies for use

during future events. While many prior major influenza research agendas and initiatives, such as the WHO Global Influenza Strategy (WHO, 2019), did not recognize this evidence-gathering need, highlighting a research gap (see Box 4-3), a number of smaller studies have examined such behavior change elements. A cross-sectional survey of the social and behavioral consequences of mask-related measures during the COVID-19 pandemic in Germany found that a mandatory face mask policy was associated with increased compliance despite only moderate levels of acceptance; mask wearing was also correlated with other positive preventive behaviors (Betsch et al., 2020). In another cross-sectional study that surveyed adults in North America and Europe about barriers and facilitators of adherence to physical distancing measures, the most frequently stated barriers included (1) streets being crowded with pedestrians, preventing efforts to keep a distance (31 percent), (2) needing to run errands for friends and family (25 percent), (3) lack of trust in government communication about the pandemic (13 percent), and (4) feeling stressed when alone or in isolation (13 percent) (Coroiu et al., 2020). Commonly endorsed motivations to engage in distancing included wanting to protect others (86 percent) or oneself (84 percent) and a sense of responsibility to protect the community (84 percent).

Compliance with non-vaccine control interventions is largely contingent upon widespread agreement that the health of a community is a public and shared good. From an evolutionary game theory perspective, the COVID-19 pandemic can be construed as a dilemma in which people are acting as "free riders" if they fail to comply. That is, they experience the benefit of their own decreased health risk as a result of other people's efforts, without actually contributing to public safety themselves and, in some cases, by actually undermining public safety (Yong and Choy, 2021). Physical distancing is a public good with an especially severe free-rider problem. The evolved human psychological tendency to eschew free-riding behaviors among others in the community could be leveraged in developing strategies to promote adherence to interventions. These might include imposing penalties for noncompliance, nurturing social norms that promote community-level cooperation (Yong and Choy, 2021), and encouraging pro-social behavior that takes advantage of the loss of social capital (Costa et al., 2021). A survey in Japan has suggested that people who have greater altruistic concerns and are more sensitive to shaming are more likely to adhere to physical distancing measures (Cato et al., 2020). In developing strategies to overcome the free-rider problem, public health officials need to consider the potential unintended consequences; for example, inducing negative feelings, such as shame, can be harmful because they also lead to self-harm, including suicide.

STRATEGIES FOR OPTIMIZING POPULATION UPTAKE OF NON-VACCINE CONTROL MEASURES

National and international responses to the COVID-19 pandemic—both successful and unsuccessful—have yielded valuable evidence and insights about potential strategies for optimizing population uptake of non-vaccine control measures during an epidemic or pandemic caused by a viral respiratory pathogen. For instance, lessons learned from social mobilization during COVID-19 include the importance of incorporating behavioral psychology principles into communication, using a trauma-responsive approach to communication, and recognizing the influence of context (e.g., no strategy is "one size fits all") (Skouteris, 2021). However, even in a public health emergency, abiding by the Siracusa Principles[3] that safeguard human rights can be a potential facilitator for uptake of control measures. In certain societies, it is important for people to be explicitly assured of the protection of their rights before they consider mandated interventions. When public health measures are enacted, certain core human rights and basic needs must still be ensured. This has been a challenge in many countries that have undergone strict lockdowns and business closures in the face of COVID-19. During and after the acute phases of a crisis, a retroactive analysis and discussion of the measures used should be conducted to ensure they were based in evidence and proportionate to the need (Sun, 2020).

The application of implementation science and frameworks could enhance the creation and uptake of non-vaccine control interventions and the management of the resource shortages that have hampered public health interventions worldwide during the COVID-19 pandemic. For example, shortages of masks made it difficult to control the spread of infections by health care workers in nursing homes in the Netherlands (Wensing et al., 2020) and in Costa Rica (Garcia et al., 2020). Challenges resulting from resource shortages could potentially have been mitigated by using implementation science principles and frameworks to enhance emergency preparedness planning. Examples include process mapping with consensus building, microplanning with simulation, and stakeholder engagement techniques (Means et al., 2020). Implementation science has also been identified as having potential to support COVID-19 mitigation efforts by evaluating an implementation context, identifying context-specific barriers, selecting strategies to increase effective delivery of an evidence-based

[3] For more on the Siracusa Principles on the Limitation and Derogation Provisions in the International Covenant on Civil and Political Rights, see https://www.icj.org/wp-content/uploads/1984/07/Siracusa-principles-ICCPR-legal-submission-1985-eng.pdf (accessed August 23, 2021).

intervention, and evaluating implementation in terms of uptake, coverage, resource efficiency, or other key measures (Chambers, 2020; Hirschhorn et al., 2020; Means et al., 2020; Wagner and Means, 2021; Wensing et al., 2020).

Ideally, policies for implementing interventions should be based on quality evidence—including testing to see how the intended audience responds, though there are limitations to the speed with which scientific evidence can be aggregated and appropriately translated into policy during a pandemic with a rapidly spreading pathogen (Williams et al., 2020). Consequently, governance and public health leadership often rely on modeling projects to inform policy development (McBryde et al., 2020), including lessons from past pandemics. More research is needed on how to rapidly create and sustainably implement evidence-based public health policy in pandemic scenarios that pose barriers to the typical process for policy development by virtue of their uncertainty and potential for loss of human health and life (Yang, 2020). Developing such policies needs to be inclusive of all relevant stakeholders and flexible enough to adapt to evolving knowledge about the pathogen and pandemic (World Bank, 2020a).

CONCLUSIONS AND RECOMMENDATIONS

Optimizing Intervention Adherence

Conclusion: The COVID-19 pandemic demonstrated that a number of contextual factors, political systems and leadership styles, culture, individual norms and beliefs, and the methods used to implement public health policies influenced the uptake and optimal execution of public health interventions. This suggests a need to conduct research to ascertain how all these factors affected public acceptance.

Recommendation 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.

Leadership and Community Engagement

Conclusion: Public trust in government officials, community leaders, scientists, and other experts, and other people who influence public opinion has affected—both positively and negatively—public response to governmental policy announcements and mandates as well as the uptake of non-vaccine interventions to slow the spread of COVID-19. Trust in such persons and confidence in what they said about interventions was undermined when the policies were shown not to rest on a strong evidence base, when the reasoning behind the policies was not well communicated, and when the personal behavior of such persons did not coherently and consistently adhere to the practices that they had recommended or required.

Recommendation 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 communicating 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").**

Data and Frameworks

Conclusion: The variety of interventions implemented in response to the COVID-19 pandemic has not always been informed by evidence of effectiveness but, in some cases, has been based on contextual factors and policy makers' individual views. This experience highlights a need to both generate evidence that is relevant across a wide range of settings and use this evidence when implementing non-vaccine control measures.

Conclusion: Historically, investments in research to evaluate strategies and means of implementing non-therapeutic and non-vaccine control measures have not been sustained over the long term. The boom-bust cycle of interest in these topics, which peaks with the onset of an epidemic or pandemic, needs to be replaced by longer-term vision and infrastructure building to enable research on all aspects of prevention and response, including non-vaccine and non-therapeutic measures.

Recommendation 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.

Recommendation 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.**

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5

Therapeutics

Until a vaccine is developed, public health countermeasures provide the major defense against a novel respiratory virus, and effective pharmaceutical and biologic agents can substantially reduce the burden that pandemics impose on individuals and health care systems. The availability of treatments—thereby reducing the need for hospitalization, shortening illness, averting death, and even preventing viral transmission—would not only reduce morbidity and mortality but also avoid harm to health care providers and patients with other diseases seen when surges in coronavirus disease 2019 (COVID-19) cases overwhelmed clinics and hospitals in country after country. However, the evidence for current pharmacological therapies for most respiratory virus infections is low to mixed. While early treatment of influenza viruses can both prevent the spread of infection to close contacts and shorten symptom duration, pharmacotherapy for respiratory viruses has otherwise largely been unsuccessful (Villamagna et al., 2020). Even potent antivirals, such as the neuraminidase inhibitors and the most recent endonuclease inhibitors, provide only a partial benefit by reducing the days of prostration and fever if begun by the first day of symptoms (Hata et al., 2014; Hayden et al., 2018).

Recent outbreaks of several novel viruses with pandemic potential—severe acute respiratory syndrome coronavirus 2 (SARS-CoV) in 2003, an H1N1 influenza virus in 2009, and Middle Eastern respiratory syndrome (MERS) in 2013—stimulated scientists to pursue effective antivirals. Yet, with the end of each outbreak, the attention of most public and private laboratories shifted to other conditions and research on antivirals faded, without having produced a collection of promising agents with established

safety data. Thus, when SARS-CoV-2 emerged in 2019, few potential antiviral compounds were available and ready to be tried (Nature Editorials, 2021). This chapter examines the role that therapeutics can play in mitigating the impact of future respiratory virus outbreaks, particularly influenza, drawing on lessons learned during the COVID-19 pandemic in the research, scale up, and use of therapeutic resources.

IMPACT OF PANDEMICS ON HEALTH SYSTEM CAPACITY

The COVID-19 pandemic has starkly exposed the extent to which a viral respiratory pathogen outbreak can overwhelm the capacity of health care systems, leaving people in need of acute and/or chronic care without access to potentially life-saving services and therapeutics. In Brazil, for example, a surge of cases in spring 2021 filled its public and private hospitals to capacity and drove shortages of sedative drugs needed to intubate COVID-19 patients in intensive care units (ICUs) (Alves, 2021). Some hospitals reported having access to just a single substitute sedative that is not typically used for intubation and may not work as effectively for that purpose, potentially causing adverse health consequences for the patients.

Beyond the impact on COVID-19 patients in need of critical acute care, outbreak-induced health system capacity issues can have life-threatening consequences for people with noncommunicable diseases or living with chronic conditions. An analysis of the impact of the pandemic on health services in multiple countries found that the Chinese National Health Commission reported reductions in outpatient visits and admissions of 21.6 percent and 16.6 percent, respectively, between January and June 2020 compared to the same period in 2019 (Tangcharoensathien et al., 2021). In Wuhan, reduced use of health services was attributed to travel restrictions and lengthy wait times for prescriptions to be filled for noncommunicable diseases. Thailand's health system was less overwhelmed during the same period, although the number of outpatient visits nonetheless declined across the country.

An evaluation of the impact of the COVID-19 pandemic on cancer care worldwide surveyed cancer care centers across 54 countries and 6 continents (Jazieh et al., 2020). The majority (88 percent) had encountered care delivery challenges, with more than half reducing their volume of services to help preemptively mitigate those challenges. Many centers reported challenges related to overwhelmed health systems (20 percent) and limited resources of personal protective equipment (PPE) (19 percent), staff (18 percent), and medications (10 percent). Almost half the centers reported that at least 10 percent of patients had missed one or more cycles of treatment. More than one-third reported that their patients had been exposed to harm due to interruptions in both cancer- and non-cancer-related care;

some centers reported that the majority (up to 80 percent) of their patients had been exposed to harm.

People living with human immunodeficiency virus (HIV) have experienced similar types of treatment interruptions and consequent impacts on health outcomes during the pandemic. A survey of more than 1,000 HIV care providers in Guangxi, China, found that many patients were unable to attend follow-up visits on schedule or obtain timely refills of their antiretrovirals, undermining their ability to adhere to treatment (Qiao et al., 2020). Providers identified a lack of patient guidance for accessing HIV services, overwhelmed clinics, and conflicts between the delivery of HIV and COVID-19 care as significant sequelae of the pandemic response.

FINDINGS, OPPORTUNITIES, AND CHALLENGES IN THE USE OF THERAPEUTIC RESOURCES DURING OUTBREAKS

This section explores the landscape of evidence, opportunities, and challenges related to the use of therapeutics during the COVID-19 pandemic and considers their potential applications to seasonal and pandemic influenza outbreaks. For the purposes of this study, the committee has defined therapeutics as the actual medications (both those directed against the virus itself and those needed to address associated symptoms and complications) and any supplies needed for their delivery, including PPE, infusion chairs, hospital beds, and ventilators. Oxygen is a particularly critical therapeutic resource for patients with severe viral respiratory diseases and can be prone to shortages, as demonstrated by the COVID-19 pandemic (Malta et al., 2021).

Strengthening Capacities to Manufacture, Mobilize, and Scale Up Therapeutic Resources

The COVID-19 pandemic has underscored the need for collaborative global efforts to prepare for future influenza events by evaluating and strengthening countries' capacities to manufacture, allocate, stockpile, mobilize, and scale up therapeutic resources.

Vulnerability of Global Supply Chains for Therapeutics

Medical product shortages can be caused by supply chain disruptions on both the demand side, such as changes in prescribing practices, stockpiling, and hoarding, and the supply side, such as manufacturing issues (Burry et al., 2020). Shortages of critical medical products that occurred at the global, national, and local levels during the COVID-19 pandemic have revealed systemic vulnerabilities and gaps within the medical product

supply chain (Miller et al., 2021). Due to the globalization of that supply chain in recent decades, manufacturing certain components that are essential to produce finished medical products has become increasingly concentrated in certain geographic regions and a relatively small number of manufacturers.

Supply chain vulnerabilities are intensified when links in the chain are overreliant on specific regions or manufacturers because a single incident—be it a natural or human-made disaster, geopolitical crisis, or pharmaceutical company's business decision—can lead to supply disruptions and shortages of therapeutics on a national or global scale. For instance, approximately 80 percent of the world's supply of active pharmaceutical ingredients (APIs) is manufactured in India and China (Burry et al., 2020). India produces large proportions of pharmaceutical finished dosage forms for the United States and many other countries, yet its pharmaceutical sector is also heavily dependent on China for up to 70 percent of its APIs (NASEM, 2021b). In Iran, greater than 95 percent of the finished dosage forms consumed are produced domestically. However, around half of the APIs used to manufacture those products is imported from China, India, and countries in Europe (Ayati et al., 2020). Even less visibility exists into the geographic concentration or reliance on sources for essential pre-API raw materials (e.g., chemical compounds, fermentation processes for antibiotics) than for APIs or finished dosage forms. Disruptions will likely continue to occur with greater frequency if production capacity is not sufficiently diversified across geographies and manufacturers.

Many lower-resource countries lack sufficient capacity to manufacture therapeutics to meet their domestic needs. For instance, only 3 percent of global drug manufacturing occurs in countries in Africa, while 70–90 percent of drugs consumed in countries in sub-Saharan Africa are imported (Bright et al., 2021). At the outset of the COVID-19 pandemic in Rwanda—where the pharmaceutical sector depends heavily on imports—interruptions to the drug supply chain resulted in widespread retail stockouts of supplies (Uwizeyimana et al., 2021). Lack of manufacturing capacity in a country can undermine its population's access to critical supplies during times of normal demand, and particularly during demand surges, but the global pharmaceutical industry often privileges the more profitable markets in higher-income countries in Europe and North America over markets in lower-income countries. During the COVID-19 pandemic, equity issues have been exacerbated as some higher-income countries—which already had greater access to pharmaceutical products—have hoarded medical supplies and halted the export of critical medical products to conserve them for domestic use (Burry et al., 2020).

Allocation and Triage of Scarce Therapeutic Resources

Due to the surge in hospitalizations and ICU admissions during the COVID-19 pandemic, hospitals and health care systems around the world faced shortages of hospital beds, oxygen, ventilators, and critical therapeutic drugs—including sedatives, analgesics, and paralytics that are often used to care for patients receiving invasive mechanical ventilation (Ammar et al., 2021; BBC News, 2021; Burry et al., 2020). In January 2021, the deaths of as many as 40 patients hospitalized with COVID-19 in Brazil were attributed to oxygen shortages; the same month, Brazilian police reported that oxygen cylinders were being illegally hoarded and sold to affluent families for their personal use (Malta et al., 2021). The United States also experienced shortages of hospital beds, ventilators, and other necessary supplies, exposing substantial gaps in the nation's health care infrastructure (*The New York Times*, 2020). In addition to shortages, situations in which therapeutics were unexpectedly underused have occurred. For example, although supply shortages of new monoclonal antibodies (mAbs) used to treat COVID-19 did occur in some areas of the United States (NGA, 2021), supplies have largely been underused in other areas of the country (Bendix, 2020). Contributing factors globally include the prohibitive cost of the treatments, the lack of specialized capacities needed to administer the therapy by infusion, and the need for patients to receive the treatment within a narrow time window after symptom onset to achieve the optimal therapeutic effect.

While this was arguably the first time this challenge of allocation during a health emergency was so widespread, it was by no means the first time communities have been faced with a patient demand that outpaced the supply. For example, following Hurricane Katrina in the Gulf region of the United States in 2005, isolated hospitals were faced with critical decisions on how to care for patients without enough resources for everyone. This austere environment and incredible burden on health care workers led to more than a decade of work on crisis standards of care. Institute of Medicine reports from 2012 and 2013 outline a systems framework for crisis standards of care and indicators and triggers to guide health care systems at all levels for use during disasters when needed, grounded in ethical and legal principles (IOM, 2012, 2013). Stakeholders well versed in crisis standards of care argue that the goal of any health care system should be to never need them. The transition from conventional to contingency to crisis care comes with a concomitant increase in morbidity and mortality, so it is important to recognize when the system is becoming overwhelmed so other mitigation measures can be put into place and avoid this transition wherever possible. It is also critical that these decisions occur before a health emergency has begun. Many public health and health care leaders have been working to engage their communities and institutional leadership to develop indicators

and triggers for shifting their standards of care across a continuum during an emergency, but it is essential that this work is more widely implemented to be best prepared for future emergencies.

Framework for Equitable Distribution of Scarce Resources

During the COVID-19 pandemic, shortages of critical therapeutics and other medical supplies repeatedly highlighted the need for conservation, allocation, triage, and distribution strategies for scarce resources, as well as evidence-based alternative and substitute therapeutic approaches. These strategies warrant difficult decisions about when and why to use scarce therapeutic resources for particular patients. However, alternative approaches may not be as safe, tolerable, or effective. For example, even if a substitute achieves an adequate level of sedation for patients receiving ventilation, it may not be commonly used in an ICU setting or may be associated with greater risks of adverse effects (Ammar et al., 2021). During shortages, strategies for distributing scarce resources warrant careful consideration to avoid exacerbating existing inequities among vulnerable populations. When oxygen was in shortage during the COVID-19 pandemic in India, inadequate capacity to distribute and deliver limited supplies of costly oxygen cylinders to health facilities in remote, rural, and low-income areas left many patients without access to the live-saving therapy (Bhowmick, 2021; McKeever, 2021). The COVID-19 Vaccines Global Access Facility experiences with equitable vaccine distribution have also highlighted challenges that could be applicable to future distribution of effective therapeutics in a pandemic should they be new or in short supply (Khoshnood et al., 2021).

Developing strategies for allocating scarce resources in a transparent, rational, and equitable way gives rise to a host of ethical implications, which have been carefully considered in frameworks developed for vaccines and therapeutics during the COVID-19 pandemic (Dejong et al., 2020; Emanuel et al., 2020; Laventhal et al., 2020; Lim et al., 2020). A National Academies consensus report released in October 2020 outlined a Framework for Equitable Allocation of COVID-19 Vaccine that used four risk-based criteria to set priorities among different population groups (NASEM, 2020):

1. Risk of acquiring infection,
2. Risk of severe morbidity and mortality,
3. Risk of negative societal impact, and
4. Risk of transmitting the infection to others.

The authoring committee developed four phases of priority allocation within the framework, focusing on underlying causes of health inequities

linked to systemic racism and the social determinants of health to mitigate the disproportionate burden COVID-19 has had on certain population groups. To strengthen preparedness for future influenza outbreaks, similar frameworks could be developed and refined in advance to guide the prioritization of scarce therapeutics using an ethical and evidence-based protocol that can be clearly communicated to public health decision makers, health care facilities, and the general public. Ideally, such a framework would be founded upon universal principles but flexible enough to be adapted based on pathogen type, mode of transmission, and evidence that emerges or evolves over the course of an influenza epidemic or pandemic. Frameworks for the equitable distribution of COVID-19 therapeutics would benefit from leveraging existing platforms for international collaboration to ensure flexible, trusted governance and engage trusted international institutions to develop, coordinate, and implement the framework (Bollyky et al., 2020). Decisions about allocation and distribution should also be shaped by accurate health surveillance data, evidence about affected populations, and information about national distribution capacities.

Stockpiling, Mobilizing, and Scaling Up Therapeutics

The global supply of therapeutics—including medications, oxygen, and various supplies needed to deliver therapeutics—must be rapidly mobilized and scaled up in a pandemic context to meet global demand. Some countries have taken steps to lift preexisting export restrictions. For instance, influenza was not as prevalent in 2020 compared to prior years, decreasing the demand for the neuraminidase inhibitor oseltamivir, an antiviral commonly used for treatment. In March 2020, India lifted restrictions to allow oseltamivir to be freely exported and repurposed for the experimental treatment of COVID-19 (Thepharmaletter, 2020). Stockpiling critical medical supplies allowed countries to meet demand on health systems to an extent during the pandemic, from national to facility levels, but most countries still appeared to be inadequately prepared to quickly scale up therapeutic resources during demand surges. Most reported inadequacies related to PPE and ventilators, with less visibility into whether countries had adequate stockpiles of other therapeutic supplies. Where other COVID-19-related shortages were reported, these extended beyond antivirals to a number of other drugs and supplies used in intensive care and hospital management (Socal et al., 2021).

In countries that had stockpiles of medical supplies, some reported challenges with adequately distributing them (Cohen and Rodgers, 2020) or even misallocating medications within a national supply chain (Kuo et al., 2021). Moreover, stockpiling can have the unintended consequences of underuse and waste of scarce resources. For instance, N95 filtering facepiece respirators were not designed to be stored for long periods, highlighting the

need for stockpile quality assurance sampling plans to complement shelf-life extension programs (Yorio et al., 2019). In Canada, the media reported that millions of expensive PPE supplies in the National Emergency Stockpile System had expired and gone to waste (Laing and Westervelt, 2020). The lack of a national centralized ordering system likely contributed to inaccurate supply and demand predictions that informed those stockpiling strategies.

Likewise, countries that depend highly on imported medical supplies, such as the United States, had difficulties maintaining and scaling up stockpiles when global supply chains and overseas manufacturing were disrupted during COVID-19 (Cohen and Rodgers, 2020; Kuo et al., 2021). Lessons learned that could bolster preparedness for future events include the need for coordinated regional stockpiles to mitigate underuse. The use of blockchain technology to forge links across supply chains and stakeholders could also help to manage stockpiles more efficiently and effectively (Bhaskar et al., 2020).

Need for International Mechanisms to Predict, Prevent, and Mitigate Shortages

No robust, agile international mechanisms or platforms exist for countries to collaborate in predicting, preventing, and mitigating shortages of therapeutics at the global and national levels. The International Health Regulations do not establish compliance, evaluation, and accountability mechanisms for essential public–private partnership functions. Existing mechanisms include the World Health Organization (WHO) voluntary Joint External Evaluations (JEE), but it occurs only every 5 years and does not provide a specific mechanism for countries to assist each other amidst resource shortages in a pandemic context (WHO, 2021). The JEE time line may provide certain checkpoints and nudges that encourage countries to invest more substantially in pandemic preparedness and response. However, the absence of an assistance mechanism for therapeutic shortages leaves countries unprepared to proactively anticipate and evaluate the efforts required to respond to pandemics rapidly and nimbly.

THERAPEUTICS PREVIOUSLY USED FOR INFLUENZA AND THOSE TRIALED IN COVID-19 WITH POTENTIAL APPLICATIONS TO PANDEMIC INFLUENZA

The COVID-19 pandemic has highlighted the dearth of knowledge and limited evidence base about treatments for severe viral respiratory infections in general. Moreover, little is known about the applicability of specific treatments across diseases caused by different respiratory pathogens, such as SARS-CoV-2 and influenza. At the end of this section, Table 5-1 provides an overview of evidence and research needs related to treatments for COVID-19 with potential applications to influenza.

TABLE 5-1 Overview of Therapeutics with Potential Application to Influenza

Treatment Category	Examples	Available Evidence and Research Needs
Antiviral agents	*Studied for COVID-19* remdesivir	• Mixed evidence for COVID-19 (recommended in the United States under National Institutes of Health [NIH] treatment guidelines for hospitalized patients on oxygen; World Health Organization guidance provides a conditional recommendation against use) • No data on influenza
	Studied for influenza oseltamivir (neuraminidase inhibitor) zanamivir (neuraminidase inhibitor) peramivir (neuraminidase inhibitor) baloxavir marboxil (endonuclease inhibitor) favipiravir (viral RNA-dependent RNA polymerase selective inhibitor)	• Oseltamivir, zanamivir, peramivir, and baloxavir marboxil approved for seasonal influenza • Need to evaluate clinical outcomes of mono- versus combination therapies on different strains of influenza • Need to further investigate additional broad-spectrum inhibitors of the RNA polymerase enzyme common to both COVID-19 and influenza • Need to explore the impact of host factors on replication of coronaviruses and influenza viruses
Monoclonal antibody (mAb) therapies	*Used for COVID-19* bamlanivimab bamlanivimab-etesevimab casirivimab-imdevimab sotrovimab *Used for Influenza A* VIS410	• Limited evidence of clinical benefit in COVID-19 patients if mAbs are administered early • Limited evidence of clinical benefit of mAbs in treating patients with uncomplicated influenza A • Need to expand the evidence base about effectiveness in treating COVID-19 and influenza, given their potential for rapid development and manufacturing

continued

TABLE 5-1 Continued

Treatment Category	Examples	Available Evidence and Research Needs
Systemic corticosteroids	dexamethasone (systemic) budesonide (inhaled)	• Evidence of improved outcomes in patients with moderate to severe COVID-19 treated with corticosteroids, but limited data on influenza • Need further data to substantiate the potential to reduce host inflammatory response in patients with severe COVID-19 and influenza both with and without cytokine inhibitors
Cytokine inhibitors	Tocilizumab Baricitinib	• Both agents currently recommended by NIH in hospitalized, hypoxic COVID patients with rapid worsening of oxygenation and/or inflammation • Effectiveness data limited for severe COVID cases, particularly patients requiring mechanical ventilation • Case report evidence of effectiveness of tocilizumab in influenza among a small number of patients taking it for other conditions, but otherwise insufficient or no data on use of either medication in influenza
Combination treatments for coinfection and secondary infections	Antibiotic agents added to antivirals	• Limited to no evidence of clinical benefit for empirically treating COVID-19 patients with antibiotics to prevent secondary infections • Studies of the prevalence of risk factors for bacterial coinfections and secondary infections in COVID-19 patients ongoing and would need to be performed for any novel pathogen

Antiviral Treatments

Several antivirals are already approved for seasonal influenza, including multiple neuraminidase inhibitors—oseltamivir, zanamivir, and peramivir—and an endonuclease inhibitor, baloxavir marboxil. Both types of agents have mechanisms of action against influenza A and B viruses: neuraminidase inhibitors block the viral neuraminidase enzyme, while the endonuclease inhibitor interferes with RNA transcription and blocks virus replication. Evidence exists that influenza antivirals can reduce mortality in severely ill patients (Muthuri et al., 2014). However, it has not yet been established whether these inhibitors are more effective alone or in combination, highlighting the need to evaluate combination treatments for different strains of influenza to prepare for future outbreaks and epidemics. Future research should target influenza and broader respiratory illnesses and be encouraged to help identify treatments for both mild and severe cases. Research should continue during the interpandemic period, with the assumption that identified treatments have a good chance of being useful against a pandemic strain.

Studies during the COVID-19 pandemic explored antiviral agents with activity against SARS-CoV-2 and the impact of combination therapies on clinical outcomes and opportunities for dose sparing; these research efforts could inform therapeutic regimens for influenza. Remdesivir was found to decrease the time to recovery in hospitalized patients with COVID-19 (Beigel et al., 2020), though no benefit was seen for mortality, need for invasive mechanical ventilation, or length of hospital stay in the WHO Solidarity trial (Pan et al., 2021; WHO Solidarity Trial Consortium, 2021). It may be more effective in combination: a randomized controlled trial (RCT) of baricitinib plus remdesivir versus baricitinib alone in hospitalized patients found that the former was more effective in reducing recovery time and improving clinical status (Kalil et al., 2021). To further elucidate the potential application of therapeutics between different viruses, it will be important to evaluate additional broad-spectrum inhibitors of RNA polymerase—an enzyme common to both SARS-CoV-2 and influenza—expanding the therapeutic options for treating coronavirus (Neogi et al., 2020; Vicenti et al., 2021) and influenza (Hayden and Shindo, 2019).

Monoclonal Antibody Therapies

These therapies rely on mAbs, which are laboratory-created proteins that function like natural antibodies and mimic the immune system's ability to defend against pathogens. In the past 30 years, mAb therapies have transformed the landscape of safe and effective treatment for a range of diseases. They hold promise for the influenza and other novel viruses, par-

ticularly because they can be developed and manufactured more rapidly than other types of therapeutics. During the COVID-19 pandemic, two mAb monotherapies and two combination therapies were developed and received Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration (FDA): bamlanivimab, bamlanivimab-etesevimab (Chen et al., 2021; Gottlieb et al., 2021), casirivimab-imdevimab (Chen et al., 2021), and sotrovimab (FDA, 2021).

Evidence about the clinical benefit of mAb therapies for COVID-19 remains relatively limited, but they have been associated with reduced hospitalizations if administered early to patients with mild or moderate symptoms at high risk of disease progression. While results have been promising for the initial strain of SARS-CoV-2, emerging research for newer variants of concern present new challenges for the efficacy (Wang, P. et al., 2021). Numerous mAb therapies are currently undergoing clinical trials to measure effectiveness, but it is not clear whether one is more effective than others or a combination might be beneficial. A Rapid Expert Consultation convened by the National Academies in early 2021 noted this as well, commenting that insufficient evidence is available to define optimal dosing or identify differential benefits and risks across various types of patients (NASEM, 2021a). The authors of that rapid report argue that current mAb therapies should not be considered standard of care for COVID-19 and called for more evidence to prioritize patients based on their likely clinical benefit and understand risk factors. Tocilizumab is another mAb therapy that has been used in treating COVID-19, but it is directed against IL-6 rather than the virus, so it is discussed below. The use of mAb therapies for influenza has also been investigated, although the evidence remains limited. An RCT examined the broadly neutralizing mAb VIS410 in treating patients with uncomplicated influenza A infection, finding that the therapy was safe and well tolerated and had beneficial impacts on symptom resolution and virus replication (Hershberger et al., 2019).

Targeting Immune Response

Another important avenue of research is host factors related to coronaviruses (de Wilde et al., 2018; Fung and Liu, 2019) and influenza (Gounder and Boon, 2019; Jones et al., 2020) that may contribute to viral replication or exacerbate a patient's response and drive disease.

Corticosteroid Treatments

Systemic corticosteroids have been used to treat patients with severe COVID-19 who develop a systemic inflammatory response; they can also be used for influenza. A prospective meta-analysis of clinical trials investi-

gating patients with severe COVID-19 found that systemic corticosteroids were associated with lower 28-day all-cause mortality compared to usual care or a placebo (WHO REACT Working Group, 2020). Inhaled corticosteroids may also have potential for COVID-19 and influenza: a multicenter RCT reported that budesonide was associated with a median 3-day reduction in time to recovery among patients at higher risk of adverse outcomes from COVID-19 (Yu et al., 2021).

Additional Immune Regulators

A systematic review of the efficacy of another COVID-19 treatment mAb therapy, tocilizumab, which targets cytokine IL-6, found that adding it to the standard of care could reduce mortality and the risk of mechanical ventilation in patients with severe disease (Aziz et al., 2021). A different systematic review found that tocilizumab has evidence of moderate certainty that it may reduce the likelihood that hospitalized patients will need mechanical ventilation, although it was not associated with a lower risk of short-term mortality (Tleyjeh et al., 2021). However, a meta-analysis of more than 10,000 patients found that IL-6 antagonist treatment resulted in a lower all-cause mortality at 28 days compared with a placebo (WHO REACT Working Group, 2021).

Baracitinib is a Janus kinase inhibitor that received EUA from FDA in combination with remdesivir, a broad-spectrum antiviral, to treat hospitalized COVID-19 patients who need supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation. It decreased time to recovery more than remdesivir alone when given in combination, particularly in patients with significant oxygen requirements (Kalil et al., 2021).

Combination Treatment for Patients with Coinfection

Antibiotics have been used to treat patients with COVID-19 who present with coinfections of other respiratory pathogens—particularly secondary bacterial pneumonia, which may also co-occur with influenza and can exacerbate disease (Contou et al., 2020; Wang et al., 2020; Zhu et al., 2020). Coinfections were commonly reported in patients during prior outbreaks of SARS-CoV and MERS-CoV, but the rate of bacterial coinfections in patients with COVID-19 is not yet well characterized, and evidence for empiric antibiotics in this clinical context remains mixed. One early study of a small number of patients found that the prevalence of any type of coinfection (both viral and bacterial) was estimated as high as 50 percent among people who died of COVID-19 (Lai et al., 2020). However, a systematic review found that only small proportions of hospitalized patients had bacterial (about 7 percent) or viral (3 percent) coinfection, suggesting

that antibiotics should not be routinely used to manage patients with confirmed COVID-19 (Lansbury et al., 2020; Oldenburg et al., 2021). The preemptive use of antibiotics in COVID-19 patients has also raised concerns about exacerbating antimicrobial resistance (Afshinnekoo et al., 2021; Jacobs, 2020; Pelfrene et al., 2021; Richtel, 2021). Preparation for future outbreaks of influenza or other novel viruses would benefit from ongoing identification and evaluation of patients most at risk of secondary bacterial infections so that empiric antibiotic use can be appropriately targeted.

Potential for Therapeutics to Mitigate Transmission

In addition to mitigating the impact of a disease, therapeutics may reduce the risk of transmitting it to close contacts—particularly if the respiratory pathogen is thought to have a high secondary attack rate, such as SARS-CoV-2. If antiviral drugs are administered early enough after the onset of symptoms, they may reduce viral shedding in the respiratory secretions and thus the risk that contacts may become infected (Mitjà and Clotet, 2020). Targeted prophylactic treatment of contacts with antivirals could confer an additional reduction in risk. Limited evidence also suggests that mAb therapies may mitigate the transmission of SARS-CoV-2 in ways that could be applicable to influenza, but more research is needed (Cohen, 2021; Wiersinga et al., 2020). However, although it has been suggested that therapies may mitigate transmission to contacts, quarantine is the only intervention that has been demonstrated to be effective in decreasing the SARS-CoV-2 contagion rate (Pascarella et al., 2020).

Self-Medication and Therapeutics Without Evidence

In an outbreak or epidemic context, the lack or scarcity of evidence-based therapeutics—coupled with misinformation and fear among the public—can drive people to self-medicate with therapeutics that are not evidence based or not indicated for the disease, with potentially deleterious effects. In the United States and some low- and middle-income countries (LMICs), such as India, some people have used nonprescribed hydroxychloroquine and chloroquine in an attempt to prevent COVID-19 (Malik et al., 2020). In other settings worldwide, particularly LMICs that lack a strong regulatory environment in health care, this has been a serious problem, resulting in private-sector businesses exploiting the public's fear, threats to health care quality, and wastage of scarce financial resources. Continued efforts to strengthen the quality of countries' health care delivery, as well as oversight mechanisms and regulatory approvals, can help to address this.

In South America, people have commonly self-medicated with ivermectin—an antiparasitic agent with antiviral effects that is often available

over the counter (Molento, 2020). Many herbal drugs have been used to treat COVID-19 in China, Pakistan, and other countries (Malik et al., 2020) without an evidence-based approach (Krouse, 2020). Self-medication has caused serious adverse effects, including mortality (CBS News, 2021). While self-medication has not been as widely documented or known for influenza, such trends could be seen with an influenza pathogen that is similarly novel and highly virulent, highlighting a need for research and availability of drugs for novel pathogens along with public education.

RESEARCH AND DEVELOPMENT OF NEW DRUGS AND REPURPOSED DRUGS

Despite multiple coronavirus outbreaks and epidemics with pandemic potential in recent decades, no effective antiviral treatments have been developed, and little progress has been made in the realm of novel therapeutics during the COVID-19 pandemic (Pagliano et al., 2021). However, a few places recognized the need for greater preparation. In 2014, the National Institutes of Health (NIH) began in vitro testing of existing drugs for potential effectiveness against several types of viruses. Its Antiviral Drug Discovery and Development Center supported studies of remdesivir, which Gilead Sciences developed for hepatitis C and respiratory syncytial virus. The drug's safety in humans was demonstrated in clinical trials during the Ebola outbreak in central Africa in 2016–2019. When SARS-CoV-2 struck, remdesivir was one of the few potential therapeutic candidates ready to be tested for clinical efficacy (Nature Editorials, 2021).

In the absence of specific antivirals with an established effect on SARS-CoV-2, many clinicians have resorted to antivirals that were developed for other types of viruses (e.g., remdesivir, lopinavir/ritonavir) and medications that are not approved as antivirals (e.g., hydroxychloroquine) (Pagliano et al., 2021). Limited evidence from clinical trials suggests that some of these repurposed therapeutics may have benefit against COVID-19, but their safety and efficacy is not yet well established; phase III clinical trials are ongoing for certain agents, including remdesivir and favipiravir (Pagliano et al., 2021).

COVID-19 has clearly established the value of maintaining government and private-sector research efforts on antiviral therapies to identify a range of drugs with established safety profiles and potential efficacy against a variety of viruses in humans. Overall, very few scientifically rigorous, large-scale evaluations exist of therapeutic approaches for COVID-19 (Saesen and Huys, 2020). However, more robust evidence is beginning to emerge about the benefits—or lack thereof—of some therapeutics through larger-scale international collaborative research efforts, such as the Randomized Evaluation of COVID-19 Therapy (RECOVERY) platform

trial, which enrolled more than 37,000 patients, and the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), with more than 5,600 patients largely recruited from the United Kingdom (Angus et al., 2020; Tikkinen et al., 2020), along with WHO's global Solidarity trial. The therapeutics being tested through that project include convalescent plasma therapy, soluble human angiotensin-converting enzyme 2, lopinavir-ritonavir, favipiravir, chloroquine and hydroxychloroquine, remdesivir, tocilizumab, and kinases. These large-scale studies have generated evidence suggesting the benefits of corticosteroids, IL-6 receptor antagonists, and anticoagulants, as well as the lack of benefits associated with treatments such as convalescent plasma, hydroxychloroquine, and lopinavir-ritonavir.

These research efforts benefit from support and coordination by international bodies in developing research platforms for rapidly testing and screening potential antiviral drugs for safety. These platforms will need to be available for rapid testing of therapeutics against novel influenza viruses. This was illustrated by the Solidarity trial, in which WHO's support facilitated broader inclusion of an international sample of patients and a flexible study architecture, which benefited from prior pragmatic trials (Gadebusch Bondio and Marloth, 2020). These features allowed for quicker and wider recruitment and expedited results and evaluations.

Limitations of Randomized Controlled Trials and Advantages of Adaptive Trial Design

The COVID-19 pandemic has exposed fundamental flaws in current clinical trial research systems and incentive structures. Due to the design of RCTs, they can be poorly suited to evaluating complex treatment and subgroup interactions. RCTs initiated in the midst of an outbreak or epidemic scenario are also often unable to generate useful evidence as quickly as needed. Many ongoing interventional studies of candidate agents are being conducted on a small scale (i.e., single-country or single-center trials) or are methodologically unsound, which limits their validity and undermines the extrapolation of their observed outcomes to other settings. Moreover, the potential application of these therapeutics to influenza remains largely unknown (Gul et al., 2020). In addition to underscoring the importance of appropriately designed RCTs aligned with a master protocol, research efforts during the pandemic have highlighted barriers to scaling up the size of these trials in a coordinated way and ensuring that lower-resource settings are better represented in study populations (Park et al., 2021). Furthermore, strategic incentives and infrastructure are needed to enable rapid sharing of anonymized data.

These and other limitations of the clinical trial research paradigm have led to calls for a shift away from the prevailing overreliance on RCTs for

demonstrating significant clinical benefit of new therapeutics in a pandemic context—a practice that has ethical and practical implications related to restricting the use of yet-unapproved therapies outside of an RCT (Keane, 2020). Developing more efficient systems for generating clinical knowledge to supplement RCT evidence could enable faster and more equitable dissemination of rational treatment innovations and approaches that are informed by evolving understanding of a pathogen. For instance, the COVID-19 pandemic has demonstrated the feasibility and value of adaptive platform trials with master protocols used worldwide.

An adaptive design approach can contribute to greater efficiency in a clinical trial—thus accelerating the development process for a therapeutic—by adjusting an ongoing trial's design and objectives based on interim results (see Box 5-1). This encourages more monitoring and evaluation in "real time" instead of waiting until trial completion. Certain treatments may be ready based on evidence in animal models or seasonal influenza, but it will be necessary to demonstrate that these work during a true influenza pandemic. For example, corticosteroids for the first SARS-CoV in 2003

BOX 5-1
Adaptive Trial Design: Opportunities and Limitations

Adaptive trial design has emerged as a leading strategy for curbing stagnation in the development of novel compounds. This approach allows for modifying the design or statistical procedures of an ongoing trial based on data collected during it. Unlike a traditional trial, an adaptive trial allows for review and adaptation processes to be nested within its implementation—before final analysis. Allowing researchers to iteratively modify trial designs can make trials more efficient, informative, and ethical, thus promoting innovation in novel drug development. These adaptations can be broadly classified into three categories: prospective, concurrent (ad hoc), and retrospective. Modifications within adaptive trial designs must be preplanned and based on data generated by the study. Adaptive trial design can afford heightened trial flexibility and efficiency by reducing sample sizes, improving the efficiency of treatment development, and increasing the chances of correctly answering clinical questions of interest. However, wider implementation will require greater clarity about when and how this type of design can be used, the implications of its use, and the interpretation and reporting its results. Logistical and regulatory barriers may limit it, for example, if funding often does not offer the flexibility required to implement it. Furthermore adaptive trial designs may not be well understood throughout the field, posing a potential barrier to peer-review processes.

SOURCES: Kairalla et al., 2012; Pallmann et al., 2018.

remained controversial and perhaps did not work well but certainly have some levels of efficacy for severe COVID-19 patients. Thus, even when treatments have levels of evidence behind them, rapid monitoring, evaluation, and potential pivoting are necessary when studying applications of novel therapeutic approaches against new pathogens.

A master protocol is an adaptive design element that is applicable across trials for evaluating different permutations of treatments and patient populations. Adaptive approaches can be used to make iterative adjustments to sharpen a study's focus on specific patient populations, clinical outcomes, and regimens that appear most promising based on the accumulating evidence of a drug's effectiveness. This approach is particularly advantageous in studies that enroll patients from multiple countries under the auspices of national health authorities. It also offers flexibility and agility in studies designed to compare interventions—such as the REMAP-CAP, RECOVERY, and Solidarity platforms—that can be adjusted or excluded based on the evolving evidence. Adaptive trial approaches could also have economic benefits; research has estimated that a design that could increase the clinical trial success rate by 4 percent could lower the overall development cost associated with a new drug by USD 0.4 billion (Mahlich et al., 2021).

However, uncertainty remains about the potential drawbacks of these approaches compared to traditional RCT design (Natanegara et al., 2020). A caveat is that the innovative trial designs require evaluation upon studies' completion to ensure the accuracy of the conclusions by validating the data and disease-severity metrics. An evaluation of multiple larger-scale RCTs that investigated COVID-19 therapeutics, including RECOVERY, Adaptive COVID-19 Treatment Trial 1 (ACTT-1), and Solidarity, found that the randomization methodologies were suboptimal for comparing matched groups according to disease severity among hospitalized patients, suggesting that improving these across trials would yield higher-quality and more robust data (Emani et al., 2021). Additionally, the lack of coordination in developing innovative research protocols has led to inefficiencies and inadequacies in many of the COVID-19 clinical trials conducted. For example, current models lack consistency in both clinical efficacy endpoints and in measurement methodologies. Building a more robust corpus of evidence about therapeutics will largely depend on sharing information more broadly through a common dataset (Natanegara et al., 2020).

Partnerships and Therapeutic Research

During the COVID-19 pandemic, incentives for the pharmaceutical industry have largely been directed toward accelerating vaccine development, but similar incentives have not been put in place for non-vaccine

therapeutics. Developing and manufacturing treatments have also been hindered by impacts of the pandemic on the global pharmaceutical industry. Among the short-term effects on the health market that have impacted the pharmaceutical sector are increases in demand for therapeutics and medical supplies—which can lead to shortages caused by panic buying and stockpiling—and changes in regulatory requirements, research and development (R&D) processes, and care delivery (e.g., the shift toward telemedicine). Longer-term impacts will likely include slowed industry growth, delays in regulatory approval, changes in consumption patterns for medical products, and the sector's shift toward a self-sufficient supply chain (Ayati et al., 2020).

The COVID-19 pandemic has demonstrated the value of public–private partnerships in therapeutic research by streamlining research efforts, development processes, and marketing authorization and broadening access. Such partnerships can facilitate international cooperation, boost regulatory agility, and serve as platforms for sharing information on product development, clinical trials, and supply chain issues (Bolislis et al., 2021). For example, the Access to COVID-19 Tools Accelerator is a cross-sectoral partnership formed by governments, private-sector businesses, civil society, and other stakeholders to advance the development and equitable distribution of medical resources during the pandemic. It was launched by the Bill & Melinda Gates Foundation, Wellcome, and Mastercard to facilitate the evaluation of new and repurposed therapeutics and vaccines, with a particular focus on expanding affordable access to those therapeutics in lower-resource settings. The International Coalition of Medicines Regulatory Authorities was convened as a forum for international collaboration by regulatory authorities; it also aims to expedite R&D for treatments and vaccines by streamlining regulatory processes (Bolislis et al., 2021). The United Kingdom developed the International COVID-19 Data Alliance, which serves as a global collaborative data platform (Health Data Research UK, 2020). However, each country presents unique challenges that should be considered in creating data-sharing platforms, and optimal representation of all interested partners is needed in the committees designed to prioritize these treatments. This goes beyond pharmaceutical stakeholders to include academic researchers and clinicians.

Moreover, the COVID pandemic has spurred the private sector to form consortia to allow cooperation and exploit synergies in research on therapeutics as well as vaccines. For example, the 23 life science companies in the COVID R&D Alliance are screening hundreds of new drugs (Nature Editorials, 2021). Nonprofit organizations, such as the Moonshot Initiative, have also been formed to convene meetings of experts and share access to high-technology equipment on a volunteer basis to pursue therapies for COVID-19 (Scudellari, 2020).

CONCLUSIONS AND RECOMMENDATIONS

Global Pandemic Preparation

Conclusion: COVID-19 illustrated critical gaps in preparation to distribute the therapeutic resources needed to care for infected patients in a respiratory viral pandemic, including antiviral medications, oxygen, and equipment necessary for the delivery of supportive care (e.g., ventilators, personal protective equipment [PPE]). Most documentation on stockpile inadequacies focused on the lack of ventilators and PPE, and there was less transparency around the adequacy of country stockpiles with regard to other therapeutic supplies.

Conclusion: COVID-19 emphasized a need to take a global view of the preparation for pandemic influenza, including the capacities of countries around the world to manufacture, stockpile, mobilize, and scale up therapeutic resources, as well as to conduct research on the effectiveness of therapeutics.

Recommendation 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.**

Pandemic Response

Conclusion: COVID-19 demonstrated the need for a framework to guide distribution of scarce and/or novel therapeutic resources in the most rational and equitable way. That framework needs to allow for adjustment based on disease prevalence, pathogen type, mode of transmission, mortality rates, and impacted populations, but universal principles will help with both insulating frontline providers from difficult resource allocation decisions and preventing health care systems from collapse.

Recommendation 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.**

Recommendation 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.

Therapeutic Research: Current Focus and Continuation During a Pandemic

Conclusion: Research during the COVID-19 pandemic has emphasized the potential benefits of "repurposed" therapeutics initially developed for another disease. Going forward, maintaining libraries of drugs that show antiviral effects and that have completed safety testing in humans could serve as a starting point for therapeutic research during a pandemic. It will also be important to test drugs—separately and in combination—that act on targets that respiratory viruses have in common (e.g., possible broad-spectrum inhibitors of RNA polymerase, an enzyme common to both COVID-19 and influenza). COVID-19 has also demonstrated the benefits of therapeutics that target exacerbated host response rather than the virus itself (e.g., steroids, tocilizumab). Continuing to evaluate host factors that might impact the severity of respiratory viral infections, either because they are required for viral replication or because they are involved in exacerbated response, could be beneficial in developing therapeutic approaches with broad applicability.

Conclusion: Open repositories, which include negative research results, need to be maintained to house these efforts, in order to identify public health measures of prevention and assessment and to ensure resources are effectively used rather than used for repeated assessment studies.

Conclusion: COVID-19 has shown the necessity of ongoing research focused on treatment of both existing and novel respiratory viruses, including those that cause seasonal and pandemic influenza, and has highlighted the success of collaborative efforts and innovative partnerships. Work done during the COVID-19 pandemic, including the Solidarity program, has demonstrated the feasibility of research efforts that integrate government programs, private companies, and public–private collaborations, and that involve research institutions cooperating internationally.

Conclusion: COVID-19 has shown the feasibility of performing rapid research on therapeutic efficacy during a pandemic through the use of adaptive platform trials with common global protocols, adding and deleting interventions in light of accumulating evidence. The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia, Randomized Evaluation of COVID-19 Therapy, and Solidarity platforms all demonstrated that this type of trial platform has many advantages, including the ability to adjust

study enrollment, include patients from many countries to achieve sufficient power to make evidence-based treatment recommendations more quickly, react to changing evidence prior to study conclusion, and compare interventions to one another, singly and in combination. Being able to build on this work could also expedite the development of evidence-based treatment guidelines when a novel pathogen is identified. In the COVID-19 pandemic, use of unproven therapeutics in an early evidence vacuum led to patient harm, which can be avoided if professional organizations and health authorities encourage clinicians to emphasize study participation from the beginning of an outbreak when previously validated therapeutic options are lacking.

Conclusion: The ability to perform adaptive trials during future pandemics could be improved by putting infrastructure in place that would allow for accelerated regulatory approvals and access to trials of therapies. This is especially important for therapeutic trials that must be conducted in multiple sites in different countries, since rounds of scientific and ethics review can otherwise take years. Establishing networks of high-quality clinical trial sites and developing and obtaining preapproval for generic study protocols from scientific and research ethics committees across all sites could allow for more rapid study enrollment and results.

Recommendation 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.

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6

Concluding Thoughts

The prediction that a severe respiratory virus outbreak could be "potentially the most devastating global health events with far-reaching consequences" (WHO, 2019a) was confirmed in 2020, which was dominated by the coronavirus disease 2019 (COVID-19) pandemic. Yet, even as parts of the world begin to overcome that pandemic and other parts struggle with surging infection due to variants of concern, the looming threat of seasonal and pandemic influenza remains. That poses the urgent question: what can be learned from the pandemic that might improve national and global response to future influenza events? One lesson is that, even with extraordinary effort and massive resources, vaccines take time to develop, test, and produce and are not a panacea for curbing a pandemic of a novel pathogen. Effective strategies to prepare for and respond to novel respiratory viruses, including influenza, must therefore also include comprehensive and coordinated surveillance to detect, trace, and quantify the virus; non-vaccine interventions to reduce viral transmission; and innovative, international means to discover and test therapeutic agents that can diminish morbidity and mortality and protect health systems and the wider society.

PRIORITIZING NON-VACCINE PUBLIC HEALTH INTERVENTIONS

Based on the study analyses, the committee reached a number of key conclusions that reaffirm the importance of non-vaccine control measures in preparing for and responding to a respiratory virus event. The committee recognized that plans should take into account a range of measures, from implementing early detection of a pathogen of pandemic potential to

lessening morbidity and mortality and from mitigating transmission during the outbreak to reducing the personal, social, and economic disruption that can be caused by public health interventions.

The study concluded that countries need to bolster surveillance capacity in order to detect cases, trace contacts, and quantify viral spread during a potential outbreak (see Table 6-1)—especially looking for currently unexpected and typically unobserved pathogens that could signal a pandemic. Many major emerging infectious disease threats—including coronaviruses and influenza viruses—have zoonotic origins at the interface of humans and wild or domesticated animals; others are shaped by environmental conditions (such as vector- and water-borne diseases) or other sources. COVID-19 underscored the need for broader implementation of collaborative and coordinated approaches (e.g., One Health) to conduct expanded surveillance at the nexus of multiple disciplines. Core surveillance capacities could also be broadened to take advantage of technological developments, such as open-access electronic data streams, digital mobility data, and sewage surveillance, all of which can provide early warning signals of disease outbreaks. Ensuring the integrity and validity of surveillance data collection and analysis is also critically important; the committee recognized that such data obtained during COVID-19 sometimes suffered from ascertainment biases and were not always collected or shared efficiently.

Non-vaccine control measures—such as face masks, distancing, and lockdowns–are used to help mitigate the spread of respiratory viruses. This study analyzed scientific evidence for the effectiveness of the most widely used measures, taking into account factors that can affect their population implementation. However, an intervention's overall effectiveness depends on both its ability to reduce virus transmission and population uptake; factors related to both need to be considered when deciding whether to recommend an intervention for a particular setting. The committee favored a layered approach in which measures are combined in a way that reduces harm to lives and livelihoods. For instance, masks are less costly than other interventions and could be recommended prior to other strategies, such as border restrictions, lockdowns, and curfews, that have wider economic ramifications in terms of job losses and disruption of people's lives. The committee recognized, though, that border restrictions and related measures were effective for some countries in holding down transmission early in the pandemic, and countries and global health agencies should consider these alongside their potential economic effects.

The committee noted that many non-vaccine control measures cannot be appropriately studied by methods conventionally considered to be "the gold standard," such as a randomized controlled trial (RCT). For instance, lockdowns cannot be imposed in a randomized fashion, and RCTs face difficulties in accounting for the myriad contextual factors that ultimately

TABLE 6-1 Study Conclusions on Surveillance (Chapter 2)

Detection of potential threats	COVID-19 has further emphasized the need to use the One Health approach to better target surveillance, including by building on currently existing platforms for influenza surveillance in wild birds, poultry, and livestock. This includes programs for detection of new zoonotic strains with pandemic potential and large antigenic drifts and shifts and research to better understand the pandemic potential of new strains.
	One Health programs need to identify new viral strains, assess the risk they pose to people, and analyze where cases are likely to be found and outbreaks are likely to begin. Interdisciplinary collaboration among U.S. agencies, academic institutions, national governments, and multilateral partners has been successful in performing this surveillance in several countries with a One Health approach.
Quantifying the spread of a pandemic	Data informing public health surveillance, including influenza and COVID-19, are vulnerable to ascertainment biases and therefore may not reflect the true underlying epidemiology; these biases happen particularly as a novel strain is first emerging. When the means used to collect data cannot be changed to avoid these problems, they can be taken into consideration during the analysis and interpretation of data being used in policy decisions. If not corrected, these biases can misinform the public about a disease's impact and the likely effects of public health interventions in general and in particular subgroups.
	Within countries, sharing of data collected from community-based surveillance is critical for identifying the likely impact of outbreaks. Inefficiencies in collecting and sharing all types and sources of data among countries and global health agencies hampered the flow of information during the COVID-19 pandemic. The rapid sharing of a wide range of data internationally, including syndromic, epidemiologic, clinical, pathogen specific (e.g., genomic), and other (such as open-source intelligence), can provide early warning of an outbreak of concern, as well as a picture of how it may develop.

continued

TABLE 6-1 Continued

Tracing the arrival and community transmission of a virus	COVID-19 showed that countries and intergovernmental bodies need to bolster their surveillance capacities, especially the ability to look for the unexpected and unobserved and sustain surveillance during disease surges. These systems can be strengthened by being repeatedly challenged to assess their ability to detect novel threats. Gaps identified can then be followed through and retested iteratively before an actual incident. Current surveillance approaches and tools are designed and more suitable for monitoring of known pandemics or ongoing surveillance for seasonal influenza than for the early detection of a pandemic-capable pathogen before widespread transmission.
	COVID-19 showed that the set of core capacities should be broadened to take advantage of technological developments, including but not limited to, digital mobility data, sewage surveillance, and monitoring of open-access electronic data streams (digital surveillance), as well as to maintain a stockpile of basic supplies (such as nasal swabs) that will be needed to conduct tests.
	Full reporting of surveillance data, to both higher authorities within a country and to international agencies, is sometimes impeded by negative political or economic repercussions. For example, disciplining local officials for reporting novel pathogens disincentivizes health surveillance. The first step in eliminating such barriers is to recognize their existence; such recognition can come from the parties involved or from observers. Unless such barriers are removed, reporting structures cannot provide complete, accurate, and timely information about possible disease outbreaks.
	Harmonization of information from multiple data sources is essential for quickly identifying the origins and spread of novel agents and strains and for providing useful information for decision makers and the public. Harmonization rests on the development and use of instruments to standardize the data. When diverse data come from many sources and reflect clinical and public health differences at the local level, particularly in the early stages of a pandemic, organizations that collect the data may be able to develop means of standardizing the data after they have been submitted.

affect the outcomes produced by different measures in diverse communities. For certain measures, science and engineering studies offer the appropriate means of obtaining valuable information about efficacy. Hence, the committee identified the need for a research framework to address the gaps in evidence for non-vaccine public health interventions that take into account the way evidence may best be assessed for each (see Table 6-2).

In analyzing the ways that responses to COVID-19 may be applicable to influenza, the committee found that face masks are not only relatively simple and inexpensive to make but, when well fitted to the wearer and containing multiple layers of materials with high filtration efficiency, very effective at reducing transmission. On the other hand, the available studies indicate that barriers and face shields worn without face masks are ineffective and hence inadvisable because they give a false sense of security and use resources that could better be devoted to improving the implementation of efficacious measures. Moreover, airflow can play a significant role with respiratory viruses, so proper building ventilation and filtration systems are critical to reducing transmission. In terms of differences in transmission, children—who usually have mild symptoms (or none) when infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and may not contribute much to the COVID-19 pandemic—are typically major factors in the spread of influenza viruses. School closures may thus be more effective in mitigating an influenza event than COVID-19. However, the ongoing emergence of variants, especially Delta in summer 2021, may change this finding.

While non-vaccine interventions are backed by scientific evidence, their successful implementation requires input from and support by multiple actors. Recommending non-vaccine control measures for a particular setting should take into account not just their effectiveness in reducing virus transmission but also the setting's culture, norms and beliefs, political systems, and other contextual factors. Recommendations should also consider the flexibility to adapt interventions that are effective in one setting but not feasible in another (e.g., physical distancing in high-density urban areas) (see Table 6-3). The COVID-19 pandemic showed the critical influence of the behavior of and communication from leaders—particularly within governments—on the population uptake of public health interventions. In many settings, trust in such elected leaders was undermined when policies did not rest on a strong evidence base or official mandates seemed to run counter to scientific findings. Countries, agencies, and organizations at the national, regional, and global levels will need to reevaluate methods for encouraging populations to adopt and follow public health measures, understanding target populations to encourage intervention uptake, instilling trust in leaders, and strengthening scientific research. The cyclical process of investigating successes and failures to improve implementation of public

TABLE 6-2 Study Conclusions on Effectiveness of Non-Vaccine Control Measures (Chapter 3)

Overarching	It is important to introduce public health interventions in combination as a layered, preventive approach to maximize the reduction in the risk of transmission. A number of factors should be considered when determining the approach that is best for a particular setting to reduce harm to livelihoods, including the effectiveness of measures in reducing viral transmission as well as economic and other contextual factors.
	There is a need for a research framework to address the gaps in evidence for particular public health interventions that takes into account that the way evidence is best assessed for each measure may differ, because some interventions cannot be tested in a RCT, that assesses measures in combination as well as separately, and that tests mandates for influenza. This should consider that some science, such as aerosol and physical sciences and engineering, provides the best evidence for specific questions and that in some cases interventions (e.g., national border closure) cannot be tested in RCTs because doing so is not feasible or ethical, so ecological or observational studies would be required. Better integrating research in these different fields can inform not only various methodologies but also more complete understanding of interventions and impacts.
Individual-level actions	Multiple lines of evidence show that face masks are effective in reducing COVID-19 transmission, and face masks should also be effective for influenza. For seasonal influenza, jurisdictions could consider a mandate depending on the setting and the incidence and severity of circulating strains. For example, masks could be mandated in hospitals during the influenza season. During a pandemic, masks should be mandated, in part because they are less costly and less disruptive than other interventions and may avert the need for a costly lockdown. The best performing masks consist of suitable materials with high filtration efficiency, fit well with no leaks, and have a low pressure drop for ease of extended use and breathability.
	Face shields are intended to be worn over masks and are used in medical settings to avoid splatter. They do not reduce exposure to aerosols. They are not a substitute for masks in the community, businesses, mass gatherings, or modes of transportation, including cars, buses, trains, ships, and airplanes. Their effectiveness when used alone is limited at best.
	Physical distancing measures, overall, have some evidence for effectiveness. Distancing of 1–2 meters reduces but does not eliminate transmission. Factors such as airflow direction, duration of exposure, and use of masks and other interventions influence the efficacy of physical distancing.
Building and environmental controls	Among the types of building and environmental controls evaluated during COVID-19 that may have applicability for influenza, ventilation/filtration systems have the most demonstrated effectiveness in reducing viral transmission. The World Health Organization (WHO) and professional organizations need to develop evidence-based guidelines for ventilation and filtration during a pandemic, and the relevant authorities in each country

	around the world need to incorporate these into their building standards. Short-term mitigation measures, such as air purifiers and information on proper use to avoid negative airflow patterns, should also be made available.
	Transparent barriers alone are effective only in the specific scenario of a brief, face-to-face interaction involving two people; in fact, barriers may be harmful because they can create "hot spots" where particles accumulate and impede proper ventilation in a room. Masks are preferred because they remove particles, whereas barriers simply divert them.
Government and public health controls	Studies during the COVID-19 pandemic produced evidence that highly restrictive, mandated measures, such as curfews and lockdowns, were effective in reducing virus transmission. They can be expected to produce similar results for influenza, but any decision to impose such measures would need to take into account their disruptive effects on personal life and the economy during the current pandemic.
	Because the SARS-CoV-2 virus had been spread by travelers to a number of countries before WHO recognized the novel coronavirus as a Public Health Emergency of International Concern—and even more so, before it declared COVID-19 a pandemic—there is little evidence that the restrictions on cross-border travel that many countries imposed were effective in reducing viral transmission during COVID-19, as is likely to be true in an influenza pandemic as well. Nonetheless, border closures—for example, by island nations—can be effective when imposed before community transmission is established, provided that any persons allowed to enter are quarantined, as should be true for all entrants who have recently been in countries where the virus is known to be present.
	There is some evidence during COVID-19 that children are not among the main drivers of SARS-CoV-2 transmission, unlike influenza, where children play a major role in community transmissibility, because they shed virus for longer and at higher levels. Hence, school closures may be more effective during an influenza pandemic at reducing transmission compared with during COVID-19; however, given the continued emergence of COVID-19 variants, such as Delta, vigilance in monitoring the transmissibility among children is needed.
	Evidence from the COVID-19 pandemic suggests that closing indoor venues, such as restaurants and churches, where people do not wear masks all the time (i.e., while eating, drinking, singing) may reduce transmission, but the emergence of recent variants of concern may influence the effectiveness of this intervention.
	For mask mandates to be effective, public health agencies need to communicate clearly with the public about the value of particular types of masks, how to use them correctly, and when and where they should be worn.
	The combination of testing, case isolation, and contact tracing has documented effectiveness for reducing transmission of COVID-19, especially when implemented early, but this strategy may be less effective for influenza due to its short incubation period. Although the evidence is incomplete, mass testing that is not targeted to groups at highest risk has not been shown to be effective in reducing viral transmission.

health interventions necessitates effective collaboration, clear communication, and strong partnerships between leaders in the domains of policy science. Hence, evidence should be generated that can be used across settings to inform, promote, and monitor intervention implementation.

If control measures fail and people become infected with a respiratory virus, the focus shifts to mitigating morbidity and mortality with therapeutic agents. COVID-19 exposed a number of critical gaps pertaining to the global capacities to stock, scale up, and allocate such drugs, including supplies needed for their delivery (see Table 6-4). This study reinforced the need to develop a framework to guide allocation of scarce therapeutic resources for patients in a health system in a way that alleviates the decision-making burden on health care providers, such as through the crisis standards of care framing referenced previously. However, these conversations need to happen well before an outbreak begins and cannot be left to chance. They require directed and focused policy shifts in research and infrastructure priorities as well as diverse community and public engagement to inform the prioritization of scarce resources.

The COVID-19 pandemic also emphasized the potential therapeutic benefits of repurposed drugs, initially developed for other diseases, and the advantages of rapid research on the efficacy of therapeutics during a pandemic via adaptive platform trials. Research efforts highlighted the feasibility and necessity of collaborative international platforms and innovative partnerships focused on developing treatments for existing and novel respiratory viruses.

A WAY FORWARD

Besides reaching conclusions and recommendations regarding preparing for future respiratory virus outbreaks, this study also brought to light important areas of work that remain to be explored and that, indeed, go beyond what we are able even to fully enumerate. Any number of reasons account for this gap in knowledge. Foremost among these is that the first response of governments, health care personnel, and scientists alike was to employ public health countermeasures against the novel coronavirus and use available therapies to treat its victims. Given the nature of the pandemic, innovation in both public policies and clinical practices quickly became a necessity, especially give the inadequacy of existing preparedness plans and the shortages in many essential supplies. But, in most settings, it took some time before such trial-and-error attempts to control the spread of the virus and respond to its effects were supplemented by explicit efforts to study what was happening and formally evaluate the effectiveness of alternative measures and policies. As the committee carried out its inquiry and prepared its conclusions and recommendations, increasing numbers of

TABLE 6-3 Study Conclusions on Implementation of Non-Vaccine Measures (Chapter 4)

Optimizing intervention adherence	The COVID-19 pandemic demonstrated that a number of contextual factors, including political systems and leadership styles, culture, individual norms and beliefs, and the methods used to implement public health policies, influenced the uptake and optimal execution of public health interventions. This suggests a need to
Leadership and community engagement	Public trust in government officials, community leaders, scientists and other experts, and other people who influence public opinion has affected—both positively and negatively—public response to governmental policy announcements and mandates and the uptake of non-vaccine interventions to slow the spread of COVID-19. Trust in such persons and confidence in what they said about interventions was undermined when the policies were shown not to rest on a strong evidence base, the reasoning behind the policies was not well communicated, and when the personal behavior of such persons did not coherently and consistently adhere to the practices that they had recommended or required.
Data and frameworks	The variety of interventions implemented in response to the COVID-19 pandemic has not always been informed by evidence of effectiveness but, in some cases, has been based on contextual factors and policy makers' individual views. This experience highlights a need to both generate evidence that is relevant across a wide range of settings and use this evidence when implementing non-vaccine control measures.
	Historically, investments in research to evaluate strategies and means of implementing non-therapeutic and non-vaccine control measures have not been sustained over the long term. The boom-bust cycle of interest in these topics, which peaks with the onset of an epidemic or pandemic, needs to be replaced by longer-term vision and infrastructure building to enable research on all aspects of prevention and response, including non-vaccine and non-therapeutic measures.

TABLE 6-4 Study Conclusions on Therapeutics (Chapter 5)

Global pandemic preparation	COVID-19 illustrated critical gaps in preparation to distribute the therapeutic resources needed to care for infected patients in a respiratory viral pandemic, including antiviral medications, oxygen, and equipment necessary for the delivery of supportive care (e.g., ventilators, personal protective equipment [PPE]). Most documentation on stockpile inadequacies focused on the lack of ventilators and PPE, with less transparency around the adequacy of country stockpiles with regard to other therapeutic supplies.
	COVID-19 emphasized a need to take a global view of the preparation for pandemic influenza, including the capacities of countries around the world to manufacture, stockpile, mobilize, and scale up therapeutic resources, as well as to conduct research on the effectiveness of therapeutics.
Pandemic response	COVID-19 demonstrated the need for a framework to guide distribution of scarce and/or novel therapeutic resources in the most rational and equitable way. That framework needs to allow for adjustment based on disease prevalence, pathogen type, mode of transmission, mortality rates, and impacted populations, but universal principles will help in both insulating frontline providers from difficult resource allocation decisions and preventing health care systems from collapse.
Therapeutics research	Research during the COVID-19 pandemic has emphasized the potential benefits of "repurposed" therapeutics initially developed for another disease. Going forward, maintaining libraries of drugs that show antiviral effects and that have completed safety testing in humans could serve as a starting point for therapeutic research during a pandemic. It will also be important to test drugs—separately and in combination—that act on targets that respiratory viruses have in common (e.g., possible broad-spectrum inhibitors of RNA polymerase, an enzyme common to both COVID-19 and influenza). COVID-19 has also demonstrated the benefits of therapeutics that target exacerbated host response rather than the virus itself (e.g., steroids, tocilizumab). Continuing to evaluate host factors that might impact the severity of respiratory viral infections, either because they are required for viral replication or because they are involved in exacerbated response, could be beneficial in developing therapeutic approaches with broad applicability.
	Open repositories, which include negative research results, need to be maintained and shared in order to identify effective public health measures of prevention and assessment and to ensure resources are effectively used rather than used for repeated assessment studies.

COVID-19 has shown the necessity of ongoing research focused on treatment of both existing and novel respiratory viruses, including those that cause seasonal and pandemic influenza, and has highlighted the success of collaborative efforts and innovative partnerships. Work done during the COVID-19 pandemic, including the Solidarity program, has demonstrated the feasibility of research efforts that integrate government programs, private companies, and public–private collaborations and that involve research institutions cooperating internationally.
COVID-19 has shown the feasibility of performing rapid research on therapeutic efficacy during a pandemic through the use of adaptive platform trials with common global protocols, adding and deleting interventions in light of accumulating evidence. The REMAP-CAP, RECOVERY, and Solidarity platforms all demonstrated that this type of trial platform has many advantages, including the ability to adjust study enrollment, include patients from many countries to achieve sufficient power to make evidence-based treatment recommendations more quickly, react to changing evidence prior to study conclusion, and compare interventions to one another, singly and in combination. Being able to build on this work could also expedite the development of evidence-based treatment guidelines when a novel pathogen is identified. In the COVID-19 pandemic, use of unproven therapeutics in an early evidence vacuum led to patient harm, which can be avoided if professional organizations and health authorities encourage clinicians to emphasize study participation from the beginning of an outbreak when previously validated therapeutic options are lacking.
The ability to perform adaptive trials during future pandemics could be improved by putting infrastructure in place that would allow for accelerated regulatory approvals and access to trials of therapies. This is especially important for therapeutic trials that must be conducted in multiple sites in different countries, since rounds of scientific and ethics review can otherwise take years. Establishing networks of high-quality clinical trial sites and developing and obtaining preapproval for generic study protocols from scientific and research ethics committees across all sites could allow for more rapid study enrollment and results.

research findings—from physical and implementation scientists, as well as from clinicians and epidemiologists—began appearing in the peer-reviewed literature. These studies have provided answers to some questions but also reveal issues—some not previously perceived—that need to be addressed. This massive amount of data that has emerged throughout the pandemic has also elucidated the need for streamlined health data from across countries that can quickly be tapped to inform decisions and policies, and ensure they are rooted in evidence and equity. Together with private-sector technology partners, the World Health Organization launched the World Health Data Hub[1] to transform data and provide a secure, transparent environment for predictive analytics and data visualization. If successful, this collaboration could be tremendously helpful during the next pandemic and help the world to avoid the lags in understanding the big picture of an outbreak, as was the case during the early months of 2020.

A second reason for the gap in knowledge is the uneven availability of scientific and financial resources among the world's nations. It is hardly surprising that most of the early research on the pandemic—and now, the first publications—came from high-income countries, even though knowing what worked well or poorly in low- and middle-income countries (LMICs) is essential. After all, ending a pandemic requires implementing effective responses in all settings around the world. Equally important, careful studies of the public health and clinical interventions used in resource-constrained settings can provide data that are also useful in making policies in wealthier settings. It is worth keeping in mind (as described in Chapter 2) that the countries with the highest health security preparedness scores on the Global Health Security Index had some of the poorest performances during the pandemic in terms of detection response times and mortality outcomes (Haider et al., 2020); this finding is in accord with the results of other preparedness assessments. Researchers should examine this disconnect to improve the ways that preparedness plans are developed and used during a pandemic and strengthen the means used to assess whether such plans are sufficient for a strong response.

The broad nature of this study's Statement of Task naturally produced some recommendations that are similarly broad. Further research is needed to analyze and expand the evidence base for each of the study topics in more detail. For example, with regard to our recommendation that surveillance systems should regularly be challenged and strengthened, more study is required to determine the best methods for doing so. In terms of formulating and executing public health policies and pandemic countermeasures, implementation science can be used to further elucidate the specific public

[1] For more on the World Health Data Hub, see https://www.who.int/news-room/feature-stories/detail/fighting-infection-with-information (accessed August 30, 2021).

health interventions that are most appropriate in particular settings and consider the logistical, social, and economic needs of specific populations. The variety of means that people use to share information (and misinformation) has challenged countries' efforts to disseminate the most current and scientifically accurate guidance to the public; further research will be needed to explore how governments can best communicate changes in policy and mandates based on the evolving evidence base. Appropriate research methodologies are needed to evaluate both public health interventions and use of new or repurposed therapeutic agents in a pandemic setting. The committee also noted the difficulty in further defining and operationalizing how to rationally and equitably distribute therapeutics; such a question merits further attention and will not have a universal answer.

It will also be important to evaluate which COVID-19-related interventions were both effective and have broader applications, including for future influenza pandemics. It is essential to remember that evidence regarding the effectiveness of many of the novel therapeutics and non-pharmacologic controls employed during COVID-19 is rapidly evolving. While reliable data remain very scarce, it would be premature to recommend interventions other than the few that rest on a solid base of evidence, such as using masks and avoiding crowded indoor spaces when the virus is still being spread widely in the community. This is especially true in settings where individual and collective resources are scarce and need to be used very wisely.

The COVID-19 pandemic has made it clear that vaccines and non-vaccine measures, including surveillance, community mitigation strategies, and communication and public outreach, are required to control transmission. While the 2017 U.S. Centers for Disease Control and Prevention Pandemic Influenza Plan does include research across several non-vaccine-related areas, many prominent research agendas and initiatives for respiratory viruses focus primarily or even solely on vaccines (CDC, 2017). For instance, WHO's 2019–2030 Global Influenza Strategy, which builds on the knowledge gaps identified in the 2010–2011 WHO Public Health Research Agenda for Influenza, does not address nonpharmaceutical interventions, which underlines the dearth of research initiatives that aim to strategically strengthen the evidence base for non-vaccine control measures for respiratory viruses (WHO, 2019b). However, community availability of COVID-19 vaccinations came more than 1 year into the pandemic. Research regarding the effectiveness of other types of interventions is therefore likely to be essential but was largely lacking at the time of this report. Furthermore, most published evidence comes from the United States and other high-income countries, demonstrating the need for similar, published studies in LMIC settings.

Defining the appropriate evidence by which to evaluate non-vaccine interventions is also complex. For instance, Chapter 3 discusses the need to

evaluate non-vaccine control measures through nonconventional methodologies, since many such measures cannot be studied in RCTs. There is considerable variation across the different contexts and settings within which public health interventions are implemented, and controlling for all such variables to conduct an RCT is not feasible. Furthermore, evaluating novel or repurposed therapeutics using RCTs during a pandemic may be neither practical nor the best way to gather evidence rapidly, given the advantages (both scientifically and ethically) of directly comparing interventions, singly or in combination, and the need for global enrollment to achieve sufficient power to draw conclusions and to make the results applicable in diverse settings. Therefore, it would be critical to consider how to overcome the challenges inherent in initiating international studies and collecting data in an outbreak or pandemic context by setting up collaborative research platforms in advance.

Around the world, countries are at various stages in the process of halting and recovering from the COVID-19 pandemic, which harshly revealed the extent to which lessons from prior epidemics were not adequately applied in policy or practice. With the devastating health, social, and economic harm wrought by the pandemic fresh in the public's mind comes an unprecedented opportunity to harness the resulting political will and public support, along with the research capacity and technological advances that were created to overcome the pandemic. As officials launch the efforts needed to prepare for the coming epidemics of novel respiratory viruses, this study demonstrates that policy makers, public health authorities, and other stakeholders should not only plan to rely heavily on non-vaccine control measures for seasonal and pandemic respiratory viruses but also support the research necessary to expand and improve such measures and the means by which they are implemented. A framework is also needed to ensure more rapid incorporation of such research results into more regularly evolving guidelines, so that history does not repeat itself with lessons that were never learned.

This report examined the crucial role of non-vaccine public health strategies in rapidly detecting, tracing, and quantifying a novel respiratory pathogen of pandemic potential when it first emerges. It has shown that, as an outbreak or pandemic evolves but before any vaccines are developed, non-vaccine interventions become the first line of defense for mitigating virus transmission. After vaccines are available, such interventions continue to be simple, cost-effective countermeasures, given that not all localities may have access to vaccines and that vaccines are not completely effective. Finally, this report highlights that when vaccines fail to deliver full protection, therapeutics are the last line of defense to avert the effects of a virus. Recognizing that the arrival of the next novel influenza or other respiratory pathogen is imminent, public health strategists at the global, regional,

and local levels need both to prioritize and to improve non-vaccine control measures now.

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Appendix A

Committee and Staff Biographies

COMMITTEE

Alexander M. Capron, L.L.B., M.A. (*Chair*), is a professor at the University of Southern California, where he teaches public health law and policy, bioethics, and torts. He occupies the Scott H. Bice Chair in Healthcare Law, Policy, and Ethics in the Gould School of Law, is a professor of medicine and law in the Keck School of Medicine, and is the co-director of the Pacific Center for Health Policy and Ethics. He previously taught at Georgetown University, the University of Pennsylvania, and Yale University. His 10 books and hundreds of articles cover a wide range of topics in law, medicine, ethics, and public health. He served as the principal rapporteur for the International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (Geneva, 2008). In 1966, he received a B.A. in economics with high honors from Swarthmore College. In 1969, he earned an L.L.B. from Yale University, where he was an officer of the *Yale Law Journal*. Mr. Capron was appointed by Congress as the chair of the Biomedical Ethics Advisory Committee and by President Clinton as a member of the National Bioethics Advisory Commission. From 1980 to 1983, he was the executive director of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, which was established by Congress and appointed by Presidents Carter and Reagan. From 2002 to 2006, he served as the director of the Department of Ethics, Trade, Human Rights and Health Law at the World Health Organization, where he co-led its global work on establishing equitable access to antiretroviral treatment

for HIV and influenza pandemics. He is an elected member of the National Academy of Medicine and the American Law Institute and an elected fellow of the American Association for the Advancement of Science and The Hastings Center. He has served as the president of the American Society for Law, Medicine, and Ethics and the International Association of Bioethics.

Patricia J. García, M.D., Ph.D., M.P.H. (*Vice Chair*), is a professor at the School of Public Health at Cayetano Heredia University (UPCH) in Lima, Peru, and a member of the National Academy of Medicine (NAM). She was the minister of health of Peru, the dean of the School of Public Health at UPCH, and the chief of the Peruvian National Institute of Health. She is recognized as a leader in global health. She is an affiliate professor with the Department of Global Health at the University of Washington and the School of Public Health at Tulane University. She is actively involved in research and training in global health, reproductive health, sexually transmitted infection/HIV, human papillomavirus, and medical informatics and has expertise in public health interventions, infectious diseases, and implementation science. Dr. García is a member of the advisory board of the Coalition for Epidemic Preparedness Innovations and the International Committee, coordinated by the NAM, that set the Statement of Task for this consensus study report. During the COVID-19 pandemic, she is leading clinical trials in Peru for SOLIDARITY, convalescent plasma, and ivermectin and has been chairing the advising governmental committee on innovations to fight the pandemic. She is active with the media providing public information about COVID-19 and other health information.

Lukoye Atwoli, M.B.Ch.B., M.Med.Psych., Ph.D., is a professor of psychiatry and the dean of the Medical College, East Africa, at Aga Khan University. He also holds visiting and honorary appointments at the Harvard T.H. Chan School of Public Health and the University of Cape Town. His current research interests center on psychiatric epidemiology, and he has carried out research on trauma and posttraumatic stress disorder (PTSD), youth and adolescent mental health, and substance use. He has also been involved in policy development and advocacy across a wide range of mental health issues and was recently appointed to chair the board of the Mathari National Mental Health Teaching and Referral Hospital, the premier psychiatric facility in the region. Dr. Atwoli obtained his medical training at Moi University in 2001 and completed his residency in psychiatry in 2006 at the University of Nairobi, both in Kenya. He was awarded a Ph.D. in psychiatry and mental health from the University of Cape Town in South Africa in 2015 with a thesis exploring the epidemiology of trauma and PTSD in South Africa. He has participated in previous workshops organized by the National Academies: Strengthening Human Resources

Through Development of Candidate Core Competencies for Mental, Neurological, and Substance Use Disorders in Sub-Saharan Africa (2013) and Providing Sustainable Mental and Neurological Health Care in Ghana and Kenya (2016).

Peter Daszak, Ph.D., is the president and the chief executive officer of EcoHealth Alliance. His research uses epidemiology and mathematical modeling coupled with field and laboratory analyses to understand infectious disease emergence, especially wildlife-origin viruses. He has worked more recently on severe acute respiratory syndrome, Nipah and Hendra, Ebola, and avian influenza viruses, while his earlier work was on wildlife diseases, including the discovery of a fungal pathogen, chytridiomycosis, causing global amphibian population declines and extinctions. His policy interests are in global health, infectious disease surveillance, emerging diseases, biodefense, public health, conservation medicine, One Health, EcoHealth, and Planetary Health. He has a keen interest in gain-of-function issues, pandemic prediction and prevention, and infectious disease threats to low- and middle-income countries.

Adolfo García-Sastre, Ph.D., M.P.S., has a research laboratory that focuses on a wide variety of viral pathogens, host–pathogen interactions, and vaccine and antiviral drug development. A major focus is influenza virus research. The lab is using both hypothesis-driven and systems biology–based approaches to understand virus pathogenesis and develop improved antivirals and vaccines. These studies are also geared toward identifying novel regulators of innate and adaptive immune responses leading to new vaccines and therapies against infectious diseases and cancer. Specifically, it is working to understand the factors associated with severe influenza virus infection, the development of pan-influenza virus vaccines, the discovery of novel adjuvants, and the use of engineered viruses as vaccine vectors and anti-tumor agents.

Denise Gray-Felder, M.A., is the founding president and the chief executive officer of the Communication for Social Change Consortium, a nonprofit organization working globally to equip people in marginalized communities, using participatory methods at the grassroots level to bring about the social change they define and need. She has held progressively more responsible communication positions during her more than 40-year career, including her current position since 2003, 4.5 years as the chief communication officer for Michigan Medicine, 9 years as a vice president of administration and the director of communication for The Rockefeller Foundation, 16 years in progressively more responsible public relations management positions at AT&T, the associate director of public relations for the United Way of Detroit, the

scriptwriter for Criminal Justice Institute-Detroit, the promotion coordinator for WKBD-TV Detroit, the editor and the publisher of community publications, a radio and television scriptwriter, and a reporter for *Lansing State Journal* (daily newspaper). Her research interests include community dialogue as a change agent; participatory communication, monitoring, and evaluation; storytelling to impact community values, attitudes, and beliefs; vaccine hesitancy/influencing anti-vax communities; HIV/AIDS communication; community radio; communication for development; health communication; and communication for social and community-level change. She has also worked with UNICEF in four northern Nigeria states on polio vaccination, the World Health Organization on tuberculosis, the West African Health Organization on neglected tropical diseases in the Sahel, WaterAid to address clean water communication in four West African countries, the International AIDS Vaccine Initiative to create initial communication plans for aids vaccines, and the GIZ on African shared values (with the African Union), community radio, and sanitation. Ms. Gray-Felder has also spent years working with Public Health Schools Without Walls, girls' education in Africa, and agricultural sciences in Africa and Asia, Green Revolution for Africa. She is a board member of the Millbank Foundation and a former appointee of the M.L. King Commission for the State of New Jersey. Her honors include the Spirit of Detroit Award and other recognitions for community service.

Gabriel Leung, M.D., M.P.H., is the 40th dean of medicine (2013–present) and the inaugural Helen and Francis Zimmern Professor in Population Health at The University of Hong Kong (HKU). He was the head of community medicine (2012–2013) at HKU, Hong Kong's first Undersecretary for Food and Health (2008–2011), and the fifth director of the chief executive's office (2011–2012) in government. Mr. Leung is one of Asia's leading epidemiologists and global health exponents. His research defined the epidemiology of three novel viral epidemics: severe acute respiratory syndrome in 2003, influenza A (H7N9) in 2013, and coronavirus disease 2019 (COVID-19). He led Hong Kong's government's efforts against pandemic influenza A (H1N1) in 2009 and served as the advisor for both the Hong Kong and mainland Chinese governments on COVID-19. He was the founding co-director of HKU's World Health Organization (WHO) Collaborating Centre for Infectious Disease Epidemiology and Control (2014–2018) and directs the Laboratory of Data Discovery for Health at the Hong Kong Science and Technology Park (2020–present). Mr. Leung regularly advises national and international agencies, including WHO, the World Bank, the Asian Development Bank, the Boao Forum for Asia, Institut Pasteur, the Japan Center for International Exchange, and the Chinese Center for Disease Control and Prevention. He is an adjunct professor at the Peking

Union Medical College Hospital and an adjunct professorial researcher at the China National Health Development Research Center. He edited the *Journal of Public Health* (2007–2014), was the inaugural co-editor of *Epidemics* and the associate editor of *Health Policy*, and is the founding deputy editor in chief of *China CDC Weekly*. He currently serves on the editorial boards of seven journals, including the *British Medical Journal*.

Chandini Raina MacIntyre, M.B.B.S., M.App.Epid., Ph.D., FRACP, FAFPHM, is a professor of global biosecurity, a National Health and Medical Research Council principal research fellow, and the head of the Biosecurity Program at the Kirby Institute, UNSW, Australia. She leads a research program in control and prevention of infectious diseases, spanning vaccinology, pandemics, bioterrorism and emerging infections, and personal protective equipment. She has led a large body of clinical trial, modeling, and experimental research on face masks and respirators for the prevention of infection. Her area of expertise is the vaccination of older adults and immunosuppressed people and the role of influenza and other infections on triggering cardiovascular events and how these can be prevented by vaccines. She is interested in surveillance for epidemics and biothreats and developed an automated, open-source, rapid epidemic observatory, Epiwatch, to detect early signals of serious epidemic or bioterrorism events. She has more than 400 peer-reviewed publications. She has received many awards, including the Sir Henry Wellcome Medal and Prize from the Association of Military Surgeons of the United States, the Public Health Association of Australia's National Immunization Award (for her research on adult vaccination), and the Frank Fenner Award for Research in Infectious Diseases.

Linsey C. Marr, Ph.D., is the Charles P. Lunsford Professor of Civil and Environmental Engineering at Virginia Tech. Dr. Marr's research interests include characterizing the emissions, fate, and transport of air pollutants to provide the scientific basis for improving air quality and health. She also conducts research on airborne transmission of infectious diseases. Dr. Marr was affiliated with the advisory board of Phylagen until January 2021 and currently consults for Smiths Detection, CrossFit, Inc., and the MITRE Corporation. She is a member of the National Academies' Board on Environmental Science and Toxicology and recently served on the planning committee for Airborne Transmission of SARS-CoV-2: A Virtual Workshop from the Environmental Health Matters Initiative and on the Committee on Grand Challenges in Environmental Engineering for the 21st Century. In 2013, she received a New Innovator Award from the National Institutes of Health director. Dr. Marr received a B.S. in engineering science from Harvard University and a Ph.D. in civil and environmental engineering from the University of California, Berkeley.

Tolbert Nyenswah, LL.B., M.P.H., is a senior research associate with the Department of International Health at the Johns Hopkins Bloomberg School of Public Health. He is an internationally recognized legal scholar and a global public health expert. Prior to joining Johns Hopkins University, he was the deputy minister of health of Liberia, the chief executive officer of the National Public Health Institute, and the assistant minister of health of the Republic of Liberia during the administration of President Ellen Johns Sirleaf, appointed by the president and confirmed by the senate three times. He specializes in health policies and systems and public health emergencies preparedness and response, advising on incident management system functionalities. He has been engaged with several public health emergencies, including as the incident manager of the 2014–2016 Ebola epidemic in West Africa, Lassa Fever, Zika, meningitis, and COVID-19. Some of his major contributions to the COVID-19 response include developing a contact tracing course that has more than 15 million viewers, including 1.1 million enrolled and certified. He has been interviewed by multiple African, North American, Asian, European, and South American media outlets, including *The Washington Post*, *The Hill*, *Business Insider*, Bloomberg, *USA Today*, NPR Radio, BBC, VOA News, World Economic Forum, *The Philadelphia Inquirer*, VOA Africa, *The New Yorker*, STAT, and Politico. He has attended and presented as an expert panelist on 2 of National Academies seminars. He is also a member of the Global Health Index International panel of experts, which assesses the overall health security capacities of nations based on a multitude of health indicators. He has received numerous awards, notably the Bloomberg Hopkins Emerging Leader, Outstanding Recent Graduate from the Johns Hopkins University Alumni Association, *TIME Magazine* Persons of the Year for Ebola Fighters in West Africa, the Medal of Excellence for Public Health Services, the Medal from the Surgeon General of the United States, and the highest Liberian civilian award for leading the Ebola crisis. He has authored and co-authored numerous scientific publications.

Rosanna Peeling, Ph.D., is currently a professor and the chair of diagnostics research at the London School of Hygiene & Tropical Medicine and the director of the International Diagnostic Centre (IDC). Trained as a medical microbiologist, she was previously the research coordinator and the head of diagnostics research at the UNICEF/United Nations Development Programme/World Bank/WHO Special Program for Research and Training in Tropical Diseases (WHO/TDR) in Geneva and the chief of the National Laboratory for Sexually Transmitted Diseases in Canada. Her research focuses on defining unmet diagnostic needs and facilitating test development, evaluation, and implementation in developing countries. She established the IDC to advocate for the value of diagnostics, foster innova-

tion, and accelerate access to quality-assured diagnostics to improve global health and combat antimicrobial resistance (AMR). She is a member of the Prize Advisory Panel for the UK Longitude Prize, the European Commission Horizon 2020 AMR Prize, and the Global AMR Innovation Fund. She contributed to WHO Testing Guidelines for HIV, hepatitis, dengue, and sexually transmitted infections and served as a member of the WHO/TDR Scientific and Technical Advisory Committee and the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics. She is a member of the Global Validation Advisory Committee for the Elimination of Mother to Child Transmission of HIV and Syphilis, the Social Innovation in Health Initiative, and the WHO COVID-19 Advisory panel for developing target product profiles for diagnostics. She is a member of the Africa Centres for Disease Control and Prevention (CDC) Laboratory Working Group for the COVID-19 Pandemic Response and has worked with the Africa CDC to set up a Biobanking Network for the evaluation of diagnostic tests for diseases of epidemic potential.

Marybeth Sexton, M.D., M.Sc., graduated summa cum laude from Georgetown University with a B.S. in biology in 2005 and summa cum laude from the Emory University School of Medicine with an M.D. in 2011. She completed an internal medicine residency at the New York Presbyterian-Columbia University Medical Center in 2014 and an infectious disease fellowship at Emory University in 2017 while also earning an M.S. in clinical research. She is now an assistant professor of infectious diseases at Emory, a health care epidemiologist for the Emory Clinic, and a member of the Serious Communicable Diseases Unit team at Emory Healthcare, with responsibilities for overseeing communicable disease response and preparedness, including for COVID-19. When the outbreak began, she was responsible for coordinating initial response efforts and developing an infrastructure that informed the creation of a health care incident command structure. She then led efforts around infection prevention policy development, care delivery, and implementation of programs for novel therapeutic agent use and vaccination. She has been responsible for policy development, implementation, and related patient and staff communication on personal protective equipment (PPE) selection, training, disinfection, and extended use protocols; universal masking and eye protection; patient and staff screening; patient visitation protocols; COVID-19 and influenza testing guidelines; contact tracing; return to work guidance for employees and patients; and efforts around recovery and safe maintenance of patient services. Her research during this time has focused on the safety and efficacy of infection control interventions, including evaluating PPE during a supply crisis and working with a multidisciplinary team to evaluate the impact of racial disparities on COVID-19 readmission.

CONSULTANT TO THE COMMITTEE

Marc Lipsitch, D.Phil., has been a global scientific leader in the epidemiology, modeling, policy, and other aspects of the COVID-19 pandemic, with more than two dozen publications and advisory roles to state, national, and global organizations. Before the pandemic, he authored more than 300 peer-reviewed publications on antimicrobial resistance, epidemiologic methods, mathematical modeling of infectious disease transmission, pathogen population genomics, immunoepidemiology of *Streptococcus pneumoniae*, vaccine trial design, and research ethics as they relate to infectious diseases. He was a co-founder of the Cambridge Working Group in 2014, whose efforts helped to initiate a pause in U.S. government funding for research involving the creation of potential pandemic pathogens, such as transmission-enhanced avian influenza strains. He is a fellow of the American Academy of Microbiology and a member of the National Academy of Medicine. He is or was on the editorial advisory boards/associate editor of *eLife*, *PLOS Medicine*, *Journal of Infectious Diseases*, *American Journal of Epidemiology*, *Epidemiology*, and *Epidemics*. He received his B.A. in philosophy from Yale University in 1991 and his D.Phil. in zoology from Oxford University in 1995. He was a postdoc with Bruce Levin at Emory University and a visiting scientist at the U.S. Centers for Disease Control and Prevention before starting as a faculty member at the Harvard T.H. Chan School of Public Health in 1999. Since 2006, he has been a professor of epidemiology, and he is the director of the Center for Communicable Disease Dynamics, which he founded in 2009.

STAFF

Ellen Schenk, Ph.D., M.P.H., was this study's director until July 2021 and a program officer with the Board on Global Health at the National Academies. She recently completed her Ph.D. with the Health Systems Program of the Department of International Health at the Johns Hopkins Bloomberg School of Public Health, where she worked on a number of projects, including studying the security situation of hospitals in Afghanistan, and traveled to Liberia during the tail end of the Ebola epidemic to work on strengthening the health system. Prior to her Ph.D., she was a fellow with the Office of Emergency Medical Services (EMS) at the National Highway Traffic Safety Administration (NHTSA), through which she interfaced with the National Academies' Forum on Medical and Public Health Preparedness for Disasters and Emergencies and did national expert consensus-building work and technical writing with the National EMS Advisory Council. While at NHTSA, she also did a detail with the Health Resources and Services Administration. She holds an M.P.H. in global health from Emory University,

where she worked with the U.S. Centers for Disease Control and Prevention and traveled to Mozambique to implement a trauma registry at Hospital Central de Maputo.

Emilie Ryan-Castillo is a senior program assistant with the Board on Global Health, working on the influenza consensus studies. She has a B.S. in public health from American University. In the past, she was a program assistant at FHI 360 and worked on diabetes prevention and childhood obesity research projects. In this role, she helped execute several large meetings, bringing together the top researchers from the U.S. Centers for Disease Control and Prevention, the National Institutes of Health, the U.S. Department of Agriculture, and the Robert Wood Johnson Foundation for the National Collaborative on Childhood Obesity Research. Recently, she served as a Rural Community Health Volunteer in Peace Corps Benin, where she worked on improving maternal health, vaccination rates, and community outreach at a local clinic in the Borgou Department.

Claire Moerder was a research associate until June 2021 working on the new influenza consensus studies while wrapping up final activities for the Forum on Global Violence Prevention and the Forum on Public–Private Partnerships for Global Health and Safety. In 2015, she graduated from Virginia Tech with a B.S. in nutrition and exercise science, did a special education teaching fellowship, and worked in the sustainable jewelry industry.

Adrienne Formentos was a research associate until July 2021 for the Board on Health Care Services at the National Academies. Prior to her work on this study, she was the research associate on The Future of Nursing 2020–2030 study and a research assistant with Knowledge Ecology International, focusing on advocacy for access to medication. She served as a volunteer with the American Red Cross on the disaster action team and case management and as the team administrator in San Francisco County. Early in her career, she was an AmeriCorps volunteer in Los Angeles, working at St. Vincent Medical Center as a patient advocate and community services coordinator, organizing health fairs and outreach to uninsured and underinsured populations. She has a dual B.A. in political science and English from Dominican University of California and an M.S. in global health from Georgetown University, where she co-led and authored a qualitative study on adolescents with mental and neurological disorders in Kintampo, Ghana.

Patricia A. Cuff, M.S., M.P.H., is a senior program officer for the Board on Global Health within the division of Health and Medicine, where she directs the Global Forum on Innovation in Health Professional Education—a

position she has held since 2012. She is also leading the U.S. Food and Drug Administration–funded study looking at mutual recognition agreements in the regulation of medicines, and a special COVID-19-related project with select academies in Africa. She worked for 11 years on the African Science Academy Development Initiative, where she was the country liaison to the Uganda National Academy of Sciences. She has directed and co-directed multiple studies at the National Academies, including *Clinical Trials During the 2014–2015 Ebola Outbreak*, *Options for Overseas Placement of U.S. Health Professionals*, and *Enhancing the Behavioral and Social Science Content of Medical School Curricula*. She joined the National Academies staff to work on the report *Emerging Microbial Threats to Health in the 21st Century*. Before going to Washington, DC, she worked at St. Luke's-Roosevelt Hospital Center in New York City in the field of HIV nutrition as a counselor, researcher, and lecturer on topics of adult and pediatric HIV. She received an M.S. in nutrition and an M.P.H. in population and family health from Columbia University and performed her undergraduate studies at the University of Connecticut.

Julie A. Pavlin, M.D., Ph.D., M.P.H., is the senior director of the Board on Global Health and board certified in preventive medicine and public health. She is a retired colonel in the U.S. Army; her previous assignments included the Armed Forces Research Institute of Medical Sciences in Bangkok, Thailand; the Walter Reed Army Institute of Research; and the U.S. Army Medical Research Institute for Infectious Diseases. After she retired from active duty, she served as the deputy director of the Armed Forces Health Surveillance Center. She concentrated most of her time with the U.S. Department of Defense in the design of real-time disease surveillance systems and was a co-founder of the International Society for Disease Surveillance.

CONSULTANTS

Anna Nicholson, Ph.D., M.A., M.Phil., is the founder and the lead writer of Doxastic, a science writing firm based in Chapel Hill, North Carolina. She created Doxastic after completing graduate degrees in linguistics, philosophy, and cognitive science at Indiana University Bloomington, Trinity College, Dublin, and University College, Dublin. Doxastic supports clients seeking to disseminate the latest advances in research, translate knowledge into improved practice and better outcomes, and shape health policy toward broader and more equitable access to care.

Megan Snair, M.P.H., is a partner and a consultant for SGNL Solutions and has more than 10 years of experience as a science writer, program director, analyst, and public health subject-matter expert. She led multiple landmark

activities and oversaw multiple scientific publications as a senior program officer and study director at the National Academies. Covering topics of national policy, infectious disease outbreaks, health system resilience, and social determinants of health, she convened more than 30 initiatives involving experts from the United States and internationally. She is adept at working with people from various backgrounds and industries and enjoys making connections in meetings that are often difficult to realize. Prior to joining the National Academies, she worked as an emergency planner for local health departments in Massachusetts and an analyst for health services of Boston Public Schools. Ms. Snair holds an M.P.H. from Boston University concentrating in epidemiology and a B.S. in biophysics from St. Lawrence University.

Peak Sen Chua is an independent consultant supporting the National Academies' activities through designing program strategy, establishing projects and initiatives, authoring detailed meeting proceedings, and advising on the drafting of various reports, publications, and case studies. Previously, he was a research associate for the National Academies, where he supported the Global Roadmap for Healthy Longevity Initiative and the Leadership Consortium for Value & Science-Driven Health System. He graduated with a B.S. in public health with a double major in political science from The George Washington University, where he also serves on the Alumni Association Executive Committee.

Sarah Anne New is an experienced science writer and educator with specific interest in global health and emergency preparedness. She is a childbirth doula and an independent consultant for SGNL Solutions. She has experience working with federal organizations, such as the U.S. Centers for Disease Control and Prevention and the U.S. Department of Homeland Security, on emergency preparedness and global laboratory capacity building. Before assuming her current positions, she was an English teacher in the Canary Islands and a senior program assistant for the Board on Global Health at the National Academies. During her time at the National Academies, she worked on two significant reports: *Crossing the Global Quality Chasm: Improving Health Care Worldwide* (2018) and *Stronger Food and Drug Regulatory Systems Abroad* (2020). Ms. New has further experience conducting research abroad and studying foreign health care systems in India, Laos, and Thailand as a Public Health Scholar at American University, where she obtained her degree in public health.

Appendix B

Public Meeting Agendas

Committee on Public Health Interventions and Countermeasures for Advancing Pandemic and Seasonal Influenza Preparedness and Response

First Committee Meeting

March 2, 4, and 5, 2021, at 8:00 p.m.–11:00 p.m. ET
Virtual Platforms

Meeting Objectives

- Conduct committee and staff introductions
- Orient the committee to the National Academies consensus study process
- Conduct the bias and conflict of interest discussion
- Hold an open session to hear from sponsoring agency on their perspective of the Statement of Task
- Hear from external speakers to get a landscape of the issues related to each task
- Discuss the Statement of Task and agree on an approach for completing the study
- Identify information needs and workplan for addressing the Statement of Task

Tuesday, March 2, 2021

CLOSED SESSION—COMMITTEE MEMBERS ONLY

OPEN SESSION

Sponsor Briefing: Discussion of the Committee's Charge

9:30 p.m. **Welcome and Introductions**
Alexander Capron, *Committee Chair*
Professor
University of Southern California

Patricia García, *Committee Vice Chair*
Professor
Universidad Peruana Cayetano Heredia

9:35 p.m. **Sponsor Perspective on Charge to the Committee**
Larry Kerr, *Sponsor*
Director, Pandemics and Emerging Threats
Office of Global Affairs
U.S. Department of Health and Human Services

9:45 p.m. **Discussion with Committee**

Speaker and Discussion on Therapeutics

10:05 p.m. **Welcome and Introduction from the Moderator**
Marybeth Sexton
Assistant Professor
Emory University

10:06 p.m. **Public Health Use of Therapeutics for Influenza Preparedness**
Matthew Wynia
Director, Center for Bioethics
University of Colorado

Frederick Hayden
Professor
University of Virginia

10:20 p.m.	**Discussion with Committee (and public, if time allows)**
11:00 p.m.	**ADJOURN OPEN SESSION AND DAY 1 OF MEETING**

Thursday, March 4, 2021

OPEN SESSION

Speaker and Discussion on Effectiveness of Non-Vaccine Control Measures

8:00 p.m.	**Welcome and Introduction from the Moderator** Raina MacIntyre Professor University of New South Wales, Australia
8:01 p.m.	**Effectiveness of Non-Vaccine Influenza Control Measures** Don Milton Professor University of Maryland Ben Cowling Professor The Hong Kong University
8:20 p.m.	**Discussion with Committee (and public, if time allows)**
8:50 p.m.	**Break**
	Speaker and Discussion on Implementation of Non-Vaccine Control Measures
9:00 p.m.	**Welcome and Introduction from the Moderator** Alex Capron Professor University of Southern California

9:01 p.m.	**Implementation Factors of Non-Vaccine Influenza Control Measures** Sheila Jasanoff Professor Harvard University Kumanan Rasanathan Former Coordinator, Health Systems, World Health Organization Cambodia (and Incident Manager, COVID-19, from March to June 2020)
9:20 p.m.	**Discussion with Committee**
9:50 p.m.	**Break**

CLOSED SESSION—COMMITTEE MEMBERS ONLY

11:00 p.m.	**ADJOURN CLOSED SESSION AND DAY 2 OF MEETING**

Friday, March 5, 2021

OPEN SESSION

Speaker and Discussion on Surveillance

8:00 p.m.	**Welcome and Introduction from the Moderator** Tolbert Nyenswah Senior Research Associate Johns Hopkins University
8:01 p.m.	**Surveillance for Influenza** Wenqing Zhang (via recorded video) Head, Global Influenza Programme World Health Organization John Simpson Deputy Director, Health Protection Directorate Public Health England
8:20 p.m.	**Discussion with Committee**
8:50 p.m.	**Break**

CLOSED SESSION—COMMITTEE MEMBERS ONLY

11:00 p.m. **ADJOURN MEETING**

Second Committee Meeting

Speaker Session Agenda on Therapeutics Research

April 22, 2021, at 4:00 p.m.–5:00 p.m. EDT

Location: Virtual
Contact: influenzapreparednesspublichealth@nas.edu

Meeting Objective

- Hear from key expertise regarding the evidence base for and process of researching novel or repurposed therapeutics for respiratory viruses during a pandemic, in particular how the experience from COVID-19 so far could strengthen future influenza preparedness.

Thursday, April 22, 2021

4:00–5:00 p.m. **EDT—OPEN SESSION**

Speakers and Discussion on Therapeutics Research

4:00 p.m.	**Welcome and Introduction from the Moderator** Marybeth Sexton Assistant Professor Emory University
4:01 p.m.	**The Evidence Base and Research for Therapeutics During a Pandemic** Christopher Seymour Associate Professor University of Pittsburgh
4:20 p.m.	**Discussion with Committee (and public, if time allows)**
4:50 p.m.	**Break and Adjourn Open Session**

Speaker Session Agenda on Implementation Science

April 23, 2021, at 7:00 a.m.–8:00 a.m. EDT

Location: Virtual
Contact: influenzapreparednesspublichealth@nas.edu

Meeting Objective

- Hear from key speakers regarding the role of implementation science frameworks with implementing non-vaccine public health interventions during COVID-19.

Friday, April 23, 2021

7:00–8:00 a.m. EDT—OPEN SESSION

Speakers and Discussion on Implementation Science

7:00 a.m.	**Welcome and Introduction from the Moderator** Patricia García Professor Universidad Peruana Cayetano Heredia
7:01 a.m.	**Implementation Science and Frameworks** Anjuli Wagner Assistant Professor University of Washington Arianna Means Assistant Professor University of Washington
7:20 a.m.	**Discussion with Committee (and public, if time allows)**
7:50 a.m.	**Break and Adjourn Open Session**

Appendix C

Study Approach

INFORMATION-GATHERING ACTIVITIES

The committee deliberated to fulfill the study's charge from March through early June 2021, with three full committee meetings during this time frame. The committee gathered information through a number of means to inform its deliberations: (1) an initial literature search to glean a landscape of the key topics related to the committee's charge, as described further in the Introduction (Chapter 1) as well as the section below; (2) the public speaker sessions at the full committee meetings, also detailed below; (3) solicitation of response to written follow-up questions from speakers at the committee meeting; and (4) written statements and information received from the public from stakeholders, which are stored in the study's Public Access File. Two of the full committee meetings involved sessions that were open to the public. The agendas of the open sessions can be found in Appendix B. The first committee meeting in March 2021 involved open sessions each of the 3 days during which eight speakers provided a general landscape of key issues on the topics related to the study Statement of Task and fielded questions from the committee. The second full committee meeting involved two open sessions during which three speakers provided commentary to the committee on specific information-gathering needs—therapeutics research and implementation science, identified in advance by the committee based on the deliberation and stage of development of the study findings, conclusions, and recommendations. The committee formed four workgroups corresponding to the first four tasks in the Statement of Task. Each workgroup also addressed research priorities, the fifth task.

Two to four committee members served as the primary members of each workgroup, based on expertise, with a committee member lead for each workgroup, mentioned in the acknowledgments. Each workgroup met twice in between each full committee meeting and corresponded offline regarding the study progress. The committee also corresponded as needed via e-mail, Zoom, and phone.

LITERATURE REVIEWS

The staff conducted an initial series of literature searches to provide to the committee a landscape of the key topics related to the Statement of Task, focused on finding information via the following databases: Scopus, Embase, Pubmed, Medline, ProQuest, Cochrane Database of Systematic Reviews, and Google Scholar. The search terms are listed below. The results obtained via these searches were screened primarily for relevance to the study's Statement of Task. Initial literature search reductions strategies focused on any systematic reviews and highly cited literature. The search terms below do not represent an exhaustive list of the searches and research carried out during the study. As described in Chapter 1, committee working groups and individual members identified priority topics related to the study Statement of Task and particular articles to consider. The resulting searches were careful but not comprehensive. More targeted literature searches were done over the course of the committee's deliberations as information needs, research gaps, and questions were identified.

Search Parameters

- Date parameters: November 2019–early June 2021
- Include international citations—foreign languages

Publication Types

Systematic reviews, rapid reviews, peer-reviewed literature, grey literature (including but not limited to federal government agencies and health science organizations), news articles, reports, case studies, clinical trials

Non-Vaccine Intervention Effectiveness Terms

covid-19 AND control AND measures AND NOT vaccines; covid-19 AND control AND measures AND social AND distancing; covid-19 AND control AND measures AND quarantine; covid-19 AND containment AND mask; covid-19 AND containment AND ventilation

Intervention Implementation Terms

SDOH - covid-19 AND "social determinants of health" OR SDOH; covid-19 AND socioeconomic; covid-19 AND class; covid-19 AND racism; covid-19 AND "health care access"; covid-19 AND poverty; covid-19 AND ("social norms" OR "social beliefs"); covid-19 AND religion; covid-19 AND custom AND culture; covid-19 AND culture AND "united states"; covid-19 AND culture AND compliance AND communal; covid-19 AND culture AND unity; covid-19 AND individualism; covid-19 AND individualism AND (partisan*)

Communication - covid-19 AND media; covid-19 AND (social media OR mass media); covid-19 AND information AND media; covid-19 AND health literacy AND health education; covid-19 AND compliance AND dissemination information; covid-19 AND implementation science; covid-19 AND science communication

Leadership and Government - covid-19 AND compliance; covid-19 AND policymaker; covid-19 AND communication AND compliance; covid-19 AND "effective communication"; covid-19 AND "trust in leadership"; covid-19 AND leadership; covid-19 AND "government actors"; covid-19 AND compliance AND trust; covid-19 AND behavior change AND education; covid-19 AND implementation AND compliance; covid-19 AND interventions AND implementation

Therapeutics Use Terms

Global AND Pandemic AND Stockpile; COVID-19 AND Therapeutics AND Stockpile; antiviral AND stockpile; COVID-19 AND Stockpile AND Barriers; COVID-19 AND Stockpile AND ventilator; pharmaceutical AND supply chain AND COVID-19; Pharmaceutical Preparations/supply AND distribution AND COVID-19/drug therapy OR COVID-19/epidemiology OR COVID-19/legislation and jurisprudence OR COVID-19/organization and administration OR COVID-19/prevention and control OR COVID-19/therapy AND Antiviral Agents AND supply and distribution; treatment AND reduced transmission AND COVID-19 AND meta analysis; therapeutics AND reduced transmission AND COVID-19 AND meta analysis; therapeutics AND COVID-19 AND transmission; monoclonal antibody therapy AND effectiveness NOT cancer; monoclonal antibodies AND COVID-19; Biomedical Research / organization & administration and COVID-19 / therapy AND Research Design; COVID-19/therapy AND Clinical Trials as Topic AND Cost-Benefit Analysis

Surveillance Terms

covid-19 AND surveillance AND challenge; covid-19 AND surveillance AND success; covid-19 AND surveillance AND innovation; covid-19 AND data AND sharing; covid-19 AND contact AND tracing; covid-19 AND testing

Research Gaps Terms

covid-19 AND research; influenza AND research; covid-19 AND research AND agenda; influenza AND research AND agenda; covid-19 AND research AND gap; influenza AND research AND gap