Research Report

AMAN J. PATEL, THOMAS MILTON, ANDREW GRAHAM, SAMUEL REYNOLDS, ULRIK HORN, JOHN TARANGELO, SASKIA POPESCU, GREG MCKELVEY, JR.

Physical Approaches to Civilian Biodefense

Identifying Potential Preparedness Measures for Challenging Biological Threats

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About This Report

This research project was initiated in response to emerging evidence on three possible biological threat scenarios that could have catastrophic effects on the United States: a fast scenario involving a rapidly spreading outbreak of a lethal human-to-human-transmissible pathogen, a silent scenario involving a pathogen that infects much of the population before infected people display visible symptoms, and a saturating scenario involving a pathogen that replicates and persists in the environment. Although these three broad scenario categories have been discussed elsewhere, the goal of this report is to better define the possibilities and limits of physical approaches to civilian biodefense against these scenarios. In this report, we offer initial frameworks for thinking about how the United States could achieve resilience against these scenarios (as well as any less severe versions), and we recommend actions that governments and civil society can take to work toward resilience. This work is not precise or conclusive; it can and should be verified and analyzed in a more detailed and expanded manner to support more-precise recommendations. This report is intended primarily for policymakers and technical staff, as well as philanthropists, who work on pandemic preparedness and catastrophic threat mitigation.

Meselson Center

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Summary

As biotechnology continues to advance—driven by progress and democratization in such fields as synthetic biology and artificial intelligence—so does its potential to improve lives. At the same time, these developments bring new challenges, including the need to responsibly manage risks associated with the release of high-consequence pathogens. To ensure national preparedness for all biological threat scenarios, no matter how severe, the United States must develop practical strategies to sustain critical functions at scale.

Our aim in this report is to probe the plausibility of protecting the United States against the following three major biological threat scenarios that challenge the United States' existing defenses:[1]

- a *fast* scenario, challenging countermeasures with a rapidly spreading outbreak of a lethal human-to-human-transmissible pathogen
- a *silent* scenario, challenging detection with a pathogen that infects much of the population before infected people display visible symptoms
- a *saturating* scenario, challenging countermeasures involving a pathogen that replicates and persists in the environment.

For each of these categories, we present a near-worst-case paradigmatic scenario but assume a near-best-case societal response with bureaucratic swiftness and wide public compliance, allowing us to assess the adequacy of existing and possible defenses independent of human and organizational behavior.

For each scenario, we set notional values for the key parameters that drive the scenario's severity. Given those parameter values, we assess numerical requirements for physical defenses that would provide capabilities relevant to protecting the U.S. population under each of these scenarios until effective pharmaceutical countermeasures could be developed and deployed. Then, we introduce one possible way that the United States could meet those requirements. Finally, we identify actions the U.S. government could take to implement that preparation in the short, medium, and long terms. Although this analysis uses the vantage point of the United States, the requirements and recommendations described here are designed to be adaptable to other countries to support their efforts to achieve resilience against catastrophic biological threats. To keep our analysis manageable, we focus on the plausibility of what we term *physical defenses*: material, nonpharmaceutical defenses within the bounds of humanity's current conceptual knowledge.

The results of our analysis for each scenario are summarized in Table S.1. Much future work is needed to refine our analysis here and potentially expand it to other scenarios, but our results suggest that physical defenses against these scenarios are indeed plausible. Targeted investments within the reach of single governments and possibly philanthropic actors can contribute to making the United States and other countries resilient to some of the most significant risks that the world may face.

[1] The scenarios are not intended to capture all possible categories of catastrophic biological threats.

TABLE S.1

Summary of Our Analysis and Recommendations for Each Scenario

	Scenario A: Fast	Scenario B: Silent	Scenario C: Saturating
Pathogen description	Airborne respiratory pathogen transmitted from human to human	Airborne respiratory pathogen with extensive presymptomatic spread	Airborne respiratory pathogen that replicates and persists in the environment
Defenses challenged	Countermeasures	Detection	Countermeasures
Physical defense strategies analyzed	Respirators and air decontamination tools	Pathogen-agnostic early detection system	Safe zones and personal protective equipment (PPE)
Worked example approach	Elastomeric half-mask respirators (EHMRs) with filtered exhalation and portable air cleaners, as well as other air decontamination tools	Short-read metagenomic sequencing of wastewater samples and long-read metagenomic sequencing of clinical nasal swabs	Positive pressure filtration–based shelters and fully encapsulating suits
Primary recommendation	Stockpile enough EHMRs to protect the vital workforce with filtered exhalation and air decontamination tools to protect all vital workplaces with 2.5 equivalent air changes per hour	(In addition to Scenario A recommendations) Sequence 145 billion short reads daily from wastewater from triturators at ten major international airports and 16 million long reads daily from 10,000 nasal swab volunteers	Prototype and test safe zone designs and answer basic questions on collective protection and PPE performance

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CHAPTER 1

Introduction

Although continued progress in biological sciences and technologies will offer more opportunities to improve human well-being in the coming decades,[1] this progress may also lower barriers that are blocking bad actors from engineering pathogens to cause destruction.[2] In extreme cases, the harms of future biological attacks may approach the magnitudes of the worst plagues of remote history—from the devastation wrought by the Black Death to the epidemics that decimated Mesoamerican societies after initial European contact.[3]

In the face of these strategic biological threats, we ask the following questions:

1. Is it possible to defend the United States against these threats?
2. If so, what can the U.S. government do to begin improving defenses against them?

This report is an initial attempt at confronting these questions. To do so, we borrow methodological inspiration from two landmark RAND papers from the 20th century: the 1946 *Preliminary Design of an Experimental World-Circling Spaceship*,[4] authored by a team of researchers at then–Project RAND, and the 1958 *Report on a Study of Non-Military Defense*, authored by Herman Kahn.[5] The former paper, written 11 years before the launch of Sputnik by the Soviet Union, examined the conceptual plausibility of earth-orbiting satellites by identifying key equations and constraints from first principles, setting numerical performance requirements given those constraints, and proposing possible designs that could meet those requirements. The latter paper follows a similar logic to explore the plausibility of protecting the U.S. population against a realized nuclear attack and provides explicit policy recommendations for doing so. Both are prime examples of the type of analysis we pursue here.

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[1] National Academies of Sciences, Engineering, and Medicine, *Safeguarding the Bioeconomy*, National Academies Press, 2020.

[2] David Luckey, Sara Duhachek Muggy, Taylor Frey, David Stebbins, Tracey Rissman, Bianca Espinosa, Daniel Tapia, Greg McKelvey, Jr., Neeti Pokhriyal, Joseph Dawson, Sara Hughes, Morgan Sandler, Rushil Bakhshi, Marta Kepe, Geoffrey Kirkwood, Sarah W. Denton, David DeSmet, Minami Makino, Ella Guest, Sina Beaghley, Suzanne Genc, Michael Miller, Skye A. Miner, Barbara Del Castello, Forrest W. Crawford, Jeffrey Lee, Clay Strickland, Sunny D. Bhatt, John Vahedi, Lydia Grek, Vanya Barrer, Ramiro Insuasti, Jr., Jack Lashendock, Derek Roberts, Aleksandr Esparza Hartunian, Shannon Walsh, Will Shumate, Elliott Brennan, Tyler Liggett, Kara Jia, Ajay K. Kochhar, James Smith, and James Ryseff, *Mitigating Risks at the Intersection of Artificial Intelligence and Chemical and Biological Weapons*, Homeland Security Operational Analysis Center operated by the RAND Corporation, RR-A2990-1, 2025; James B. Petro, Theodore R. Plasse, and Jack A. McNulty, "Biotechnology: Impact on Biological Warfare and Biodefense," *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*, Vol. 1, No. 3, September 2003; Jan van Aken and Edward Hammond, "Genetic Engineering and Biological Weapons," *EMBO Reports*, Vol. 4, Supp. 1, 2003.

[3] Saloni Dattani, "What Were the Death Tolls from Pandemics in History?" Our World in Data, December 7, 2023.

[4] F. H. Clauser, *Preliminary Design of an Experimental World-Circling Spaceship*, Douglas Aircraft Company, RAND Corporation, SM-11827, 1946.

[5] RAND Corporation, *Report on a Study of Non-Military Defense*, R-322-RC, 1958.

Our analysis starts in Chapter 2 with goal-setting: describing the broad defense objective we aim to achieve throughout the report (protecting U.S. critical functions). In Chapter 3, we detail the scope of our analysis: the technical plausibility of what we term *physical defenses* (nonpharmaceutical countermeasures that require material goods) assuming a best-case societal response, and the three scenarios we consider and the assumptions we make across them. In Chapters 4–6, we analyze each scenario in detail. We model default outcomes under existing defenses, discuss possible approaches to improve physical defenses, and derive key equations governing the success of those approaches. We then use those equations to set rough numerical requirements for physical defenses, describe one possible way to meet those requirements, and offer recommendations and policy options for implementing that possible solution. Finally, in Chapter 7, we conclude with a discussion of the limitations of this analysis that future work could address.

CHAPTER 2

Maintaining Critical Functions

Chapter Summary

Ensuring that the United States remains resilient against biological threats requires that the U.S. population has sustained access to fundamental inputs for human survival. This chapter reviews these inputs at the individual and population levels, the functions required to provide these inputs, and the workforce necessary to operate those functions. We examine how these functions are vulnerable to biological threats, which could trigger cascading failures that jeopardize public survival and national stability.

Defining Critical Functions

The *minimum inputs* to the survival and health of an individual human are air, water, and food; systems to manage human outputs from excretion, respiration, and perspiration; and maintenance of appropriate environmental conditions.[1] Without access to air, humans will die in about three minutes; without water, about three days; and without food and nutrition, three weeks to three months. These inputs must also be sufficiently free from contamination with toxic substances or pathogens that could cause disease.

Modern American society relies on many interconnected functions to provide these individual human inputs to its population of about 340 million people.[2] The following is just one simplistic example of the interdependencies between these functions:

- Humans require food to survive.
- To grow enough calories to feed the U.S. population, farmers depend on chemical processing functions that can produce ample fertilizer.
- To produce enough fertilizer, chemical processing plants depend on electricity generation and transmission functions to run the Haber-Bosch process that converts atmospheric nitrogen into usable ammonia.[3]
- To generate enough electricity, power utilities depend on fuel production and distribution functions that can provide large quantities of fuel.
- To produce and distribute fuels, fuel companies depend on transportation functions based on vehicles and pipelines.

[1] National Aeronautics and Space Administration (NASA), Office of the Chief Health and Medical Officer, *Environmental Control & Life Support System (ECLSS): Human-Centered Approach*, NASA-STD-3001 Technical Brief, November 14, 2023.

[2] U.S. Census Bureau, "U.S. and World Population Clock," webpage, last updated July 31, 2025.

[3] Jan Willem Erisman, Mark A. Sutton, James Galloway, Zbigniew Klimont, and Wilfried Winiwarter, "How a Century of Ammonia Synthesis Changed the World," *Nature Geoscience*, Vol. 1, October 2008.

- To ensure the reliability and security of transportation systems, countries require effective telecommunications functions to coordinate operations and law enforcement functions to prevent piracy or robbery.

For this analysis, we use the National Critical Function (NCF) set defined by the Cybersecurity and Infrastructure Security Agency to identify and categorize these important functions. This set describes 55 capabilities that the United States must maintain to prevent the debilitation of national security and public health.[4]

Although we primarily refer to the NCFs in this analysis, the U.S. government has also developed other frameworks for important societal functions, such as the National Essential Functions that enumerate the U.S. government's priorities during large-scale disaster response and the Primary Mission Essential Functions that agencies must continually perform (and that federal Continuity of Operations Programs aim to protect).[5]

Large-scale biological attacks could cause much of the U.S. workforce to be simultaneously incapacitated or unwilling to work because of fear or the need to care for loved ones, which would, in turn, affect the country's ability to maintain the continuity of these NCFs, execute a successful national response to the threat, and preserve the President's command and control under all circumstances (Figure 2.1). These effects would then feed back into the magnitude and severity of the threat, increasing the difficulty of providing clean air, food, and water to the United States and meeting the U.S. government's resilience goals and its obligation under Article III of the North Atlantic Treaty to maintain its ability to resist armed attack.[6] Adversarial attacks could be optimized for disrupting the NCFs by being conducted in a manner that muddles a coordinated response, evades existing defenses, or aims for a small number of NCF failures that are likely to lead to cascading failure of other NCFs.[7]

Defining the U.S. Vital Workforce

The core priority of preparing for such scenarios is to preserve the U.S. workforce required to operate NCFs, no matter the nature of the biological threat. We term these workers *vital workers* (VWs). Keeping these VWs alive and healthy for the duration of a biological threat scenario is a priority for preventing NCF failure. For the purposes of the modeling in this report, we use "preventing more than 50 percent of VWs from being incapacitated" as the goal that defenses should aim toward. This is an arbitrary threshold meant to simplify the calculations in this report. Protecting 100 percent of VWs is likely not strictly necessary because NCF operators likely have enough flex capacity to handle a small fraction of VWs being absent, but protecting more than single-digit percentages of VWs is likely necessary to keep NCFs operational. We therefore chose 50 percent of VWs as a convenient midrange protection target. This number can be scaled up or down

[4] Cybersecurity and Infrastructure Security Agency, "National Critical Functions Set," webpage, U.S. Department of Homeland Security, undated.

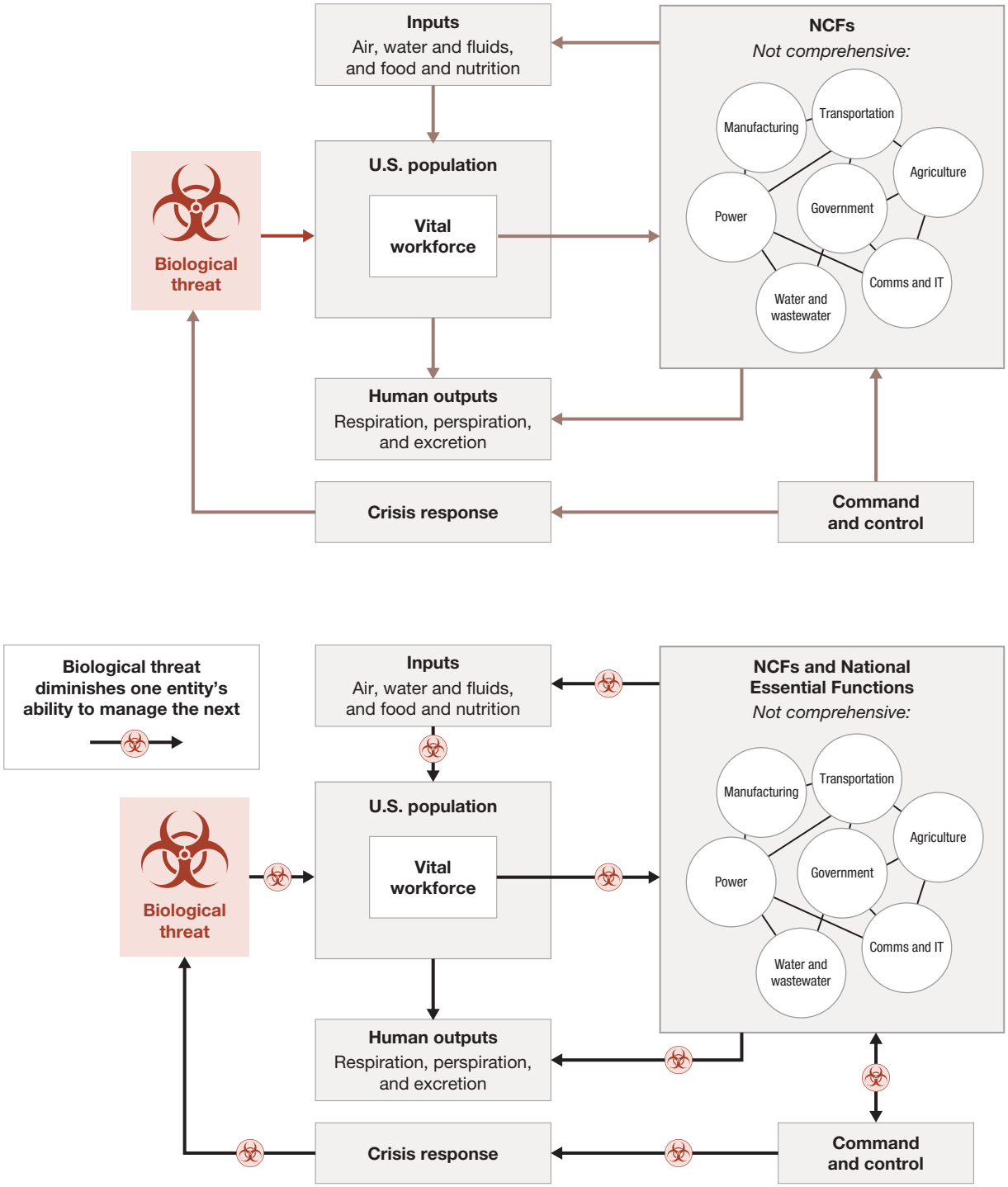
[5] George W. Bush, *National Continuity Policy*, National Security Presidential Directive 51, Homeland Security Presidential Directive 20, Executive Office of the President, May 4, 2007; U.S. Department of Homeland Security, "List of Validated Primary Mission Essential Functions (PMEFs) by Department," last updated April 10, 2025.

[6] Joseph R. Biden, *National Security Memorandum on Critical Infrastructure Security and Resilience*, National Security Memorandum 22, Executive Office of the President, April 30, 2024; The North Atlantic Treaty, signed at Washington, D.C., April 4, 1949.

[7] Dongli Duan, Changchun Lv, Shubin Si, Zhen Wang, Daqing Li, Jianxi Gao, Shlomo Havlin, H. Eugene Stanley, and Stefano Boccaletti, "Universal Behavior of Cascading Failures in Interdependent Networks," *Proceedings of the National Academy of Sciences*, Vol. 116, No. 45, November 5, 2019.

FIGURE 2.1

Feedback Loops Among Biological Threats, National Critical Functions, and Government Response Capacity



NOTE: Comms = communications; IT = information technology.

in future extensions of this work, although it is worth noting that while some costs scale linearly with the number of VWs to be protected, others do not.

There is a substantial literature debating how much ruin a state can bear before it ceases to exist,[8] but the underlying reality remains constant: Prolonged NCF failure is unacceptable. In many areas of the United States, there are simply not enough natural resources for the population to "live off the land" forever without industrialized food and water distribution, and some threat scenarios (such as Scenario C) preclude this possibility anyway. If NCFs begin to fail at providing population-scale human inputs, the communities, everyday interactions, and cultural traditions that make up the United States will wither.

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[8] Herman Kahn, *On Thermonuclear War*, Transaction Publishers, 2007; Herman Kahn, "Thinking About the Unthinkable," *Naval War College Review*, Vol. 15, No. 8, 1962.

CHAPTER 3

Identifying Challenging Scenarios

Chapter Summary

In this chapter, we identify scenarios that could threaten to compromise critical functions. To do so, we first examine the high-level categories of defenses that are typically employed to counter biological threats. We then choose to probe *physical defenses*—specifically, nonpharmaceutical, material defenses, as opposed to pharmaceutical or behavioral defenses—and identify possible scenarios that could challenge existing defenses in each of those intervention categories. We define numerical parameters that can be tuned to establish a canonical scenario in each scenario category and describe assumptions to simplify the analysis in following chapters.

Categories of Defenses

Over centuries of disease outbreaks, humanity has developed a wide-ranging set of tools for reducing public harm and protecting important societal functions during epidemics and pandemics. Broadly, these defenses fall into two main buckets: *detection* and *countermeasures*. *Detection* involves identifying the presence and severity of circulating pathogens, and *countermeasures* aim to control the scale of harm caused by pathogens. Although many countermeasures are usually deployed only after a threat has been detected, some can feasibly be deployed before detection. We can further divide countermeasures into two main subcategories: *nonpharmaceutical countermeasures* that generally prevent exposure and infection and *pharmaceutical interventions* that generally prevent severe disease once humans have been exposed and infected.

In Table 3.1, we list some of the defenses that could help protect individuals in a biological threat scenario. We borrow some elements from the "hierarchy of controls" used by industrial hygiene professionals to delineate interventions used to reduce workers' exposure to hazards (including biological ones).[1]

In this report, we focus on the technical plausibility of what we term *physical defenses*: nonpharmaceutical countermeasures that require material goods, unlike behavioral defenses that are dependent more on public will than science. We exclude pharmaceutical countermeasures, which dominate existing biodefense efforts,[2] because effective pharmaceutical countermeasures are unlikely to be available in the early stages of an outbreak. Most pharmaceutical countermeasures are generally effective only against single pathogens or a small number of pathogens. Any stockpiled pharmaceuticals likely will be ineffective against future outbreaks of

[1] National Institute for Occupational Safety and Health, "About Hierarchy of Controls," webpage, Centers for Disease Control and Prevention, April 10, 2024.

[2] Office of the Assistant Secretary for Preparedness and Response, *Public Health Emergency Medical Countermeasures Enterprise: Multiyear Budget: Fiscal Years 2023–2027*, U.S. Department of Health and Human Services, March 15, 2024.

TABLE 3.1

Common Interventions to Prevent Vital Worker Incapacitation from Biological Threats

Defense Category	Intervention	Generic Description	Applications in a Biological Threat Scenario
Detection		Identifying an active hazard.	• Alerting authorities to an actively spreading pathogen and the potential need for deploying additional countermeasures[a]
Countermeasures (nonpharmaceutical)	Elimination	Physically removing a hazard from a particular space.	• Screening and preventing infectious individuals or materials from entering a space, including via source control[b]
	Engineering controls	Reducing or eliminating exposure to hazards by modifying environments or isolating hazards from individuals.	• Decontaminating surfaces and air in occupied indoor spaces – Surface decontamination methods include surface disinfection and choosing self-disinfecting surfaces. – Air decontamination methods include ventilation, filtration, and air disinfection.[c]
	Administrative controls	Reducing exposure to hazards through procedural or policy-based measures.	• Stay-at-home orders, social distancing requirements, adherence to standard operating procedures, and other processes or policies that modify human behavior and contact patterns[d]
	Personal protective equipment (PPE)	Reducing exposure to hazards through equipment that individuals can wear.	• Barrier PPE and respirators – *Barrier PPE* includes gloves, gowns, face shields, goggles, and other wearables. – *Respirators* are wearable devices that deliver cleaned air to wearers. • Some types of barrier PPE and respirators can also perform elimination functions via source control.[e]
Countermeasures (pharmaceutical)	Vaccines	Biological substances that stimulate immunity to pathogens.[f]	
	Therapeutics	Drug products that treat or cure disease.[g]	

NOTE: Physical defenses are indicated in *italic* type.

[a] C. Raina MacIntyre, Samsung Lim, Deepti Gurdasani, Miguel Miranda, David Metcalf, Ashley Quigley, Danielle Hutchinson, Allan Burr, and David J. Heslop, "Early Detection of Emerging Infectious Diseases—Implications for Vaccine Development," *Vaccine*, Vol. 42, No. 7, March 2024.

[b] Australian Government Department of Health and Aged Care, "Infection Prevention and Control Expert Group—The Hierarchy of Controls for Minimising the Risk of COVID-19 Transmission," September 27, 2022.

[c] Curtis J. Donskey, "Continuous Surface and Air Decontamination Technologies: Current Concepts and Controversies," *American Journal of Infection Control*, Vol. 51, No. 11S, November 2023.

[d] Technical Resources, Assistance Center, and Information Exchange, "Hospital Operations Toolkit for COVID-19," U.S. Department of Health and Human Services, last updated September 2021.

[e] Gryphon Scientific, *Towards a Theory of Pandemic-Proof PPE*, Blueprint Biosecurity, June 2024.

[f] National Institute of Allergy and Infectious Diseases, "Vaccines," webpage, National Institutes of Health, last updated December 17, 2024.

[g] National Institute of Allergy and Infectious Diseases, "Therapeutic Development Services," webpage, National Institutes of Health, last updated April 28, 2025.

novel pathogens, especially future pathogens that are deliberately engineered to evade existing pharmaceutical countermeasures.[3] Thus, pharmaceutical countermeasures may need to be designed, approved, and mass-manufactured from scratch after an outbreak is detected, so it would be unwise to rely on the availability of effective pharmaceuticals to protect society immediately. Fundamental breakthroughs in pharmaceutical design and biomanufacturing would likely be necessary to enable rapid availability of effective pharmaceuticals during a novel outbreak.

By limiting our scope to the physical defenses within our existing conceptual knowledge, we avoid relying on the occurrence of future breakthroughs that would be necessary to make pharmaceutical countermeasures a reliable option for defense.

Defining Threats That Challenge Existing Defenses

We identify three scenarios characterized by biological threats that challenge physical defenses:

- Scenario A challenges countermeasures with a fast-moving human-to-human transmitted pathogen.
- Scenario B challenges detection with a novel human-to-human transmitted pathogen with extensive presymptomatic spread.
- Scenario C challenges countermeasures from another angle with a pathogen that replicates in the environment but can still infect humans.

To construct these scenarios, we borrow a standard risk management practice (used in engineering and other disciplines) of using *safety margins*: using severe scenarios to set performance requirements for defenses such that those defenses will also perform adequately in less severe scenarios. To this end, we identify numerical parameters relating to the pathogen and its dynamics that determine the severity of each scenario. In the following chapters, we then tune these parameters in each scenario to near-observed limits. In all scenarios, we also assume the pathogen has a 100-percent infection fatality rate. In nature, this rate is approached by such pathogens as untreated furious rabies and pneumonic plague.[4]

Although we are not confident that pathogens with these characteristics are biologically plausible, especially alongside the other parameters set in each scenario, ensuring that physical defenses can handle these severe cases provides an additional buffer in less severe scenarios.

Cross-Scenario Assumptions

We analyze physical defenses while assuming that behavioral and pharmaceutical interventions are deployed to the maximum extent plausible with existing technology, and that human and organizational behavior are around maximally efficient and cooperative. In other words, we focus on the question: Do current physical defenses suffice to address the near-worst-case scenarios that we describe, even if we assume a near-best-case societal response?

In the following section, we discuss how we apply this assumption across all scenarios.

[3] Joseph Torresi, Sarah McGuinness, Karin Leder, Daniel O'Brien, Tilman Ruff, Mike Starr, and Katherine Gibney, "Non-Vaccine-Preventable Infections," in *Manual of Travel Medicine*, 4th ed., Springer, 2019.

[4] Alex P. Salam, Amanda Rojek, Erhui Cai, Mihaja Raberahona, and Peter Horby, "Deaths Associated with Pneumonic Plague, 1946–2017," *Emerging Infectious Diseases*, Vol. 26, No. 2, October 2020; World Health Organization, "Rabies," webpage, June 5, 2024a.

Administrative Controls, Government Swiftness, and Public Compliance

To keep our focus on material goods, we assume that administrative controls that approximate the upper bound of successful response actions are immediately applied on disease detection with full public compliance. We assume that symptomatic surveillance is sufficiently effective to detect the disease and recognize its significance immediately after the first death. After detection, the administrative controls applied include the following:

- Except for VWs, the public does not have any in-person contact with others outside their households. (Essential activities, such as food distribution, happen through such low-contact methods as delivery to household doorsteps.)
- The use of PPE is enforced in all workplaces where VWs spend time.

Although these policies are unlikely to have full compliance in the real world, similarly strict policies were approached in China, New Zealand, and Singapore during the coronavirus disease 2019 (COVID-19) pandemic. During China's "zero COVID" controls from 2020 to mid-November 2022, the national and local governments enacted frequent stay-at-home orders in major cities, internal and external travel restrictions, thorough contact tracing, mandatory quarantining of households with positive tests, and *closed-loop management* of some communities and industrial facilities that prohibited exiting the area without wearing a mask or respirator or entering without passing an infection screening.[5] We assume that all relevant government authorities are extremely swift at implementing these controls once a threat has been detected.

We also assume the only reason that VWs are absent from work is illness and death. There is no absenteeism because of fear of infection or caregiving, although such fear would likely lead to significant absenteeism in a real event.[6] In the three scenarios we analyze, these assumptions allow us to consider required physical defenses independent of human or organizational behavior.

Pharmaceutical and Diagnostic Capabilities

To keep our focus on nonpharmaceutical defenses, we assume the existence of the ambitious *100 Days Mission* capabilities aimed for in the 2022 *National Biodefense Strategy* (NBS),[7] in which "a candidate vaccine is developed within 100 days after determination of a potentially significant biological threat," and enough vaccines are available for the entire U.S. population 30 days after approval. We assume the 130-day clock begins immediately after the first death from the outbreak.

The success of the 100 Days Mission depends on uninterrupted pharmaceutical development and production and no large-scale disruptions to NCFs. The primary challenge for physical defenses is to prevent infections in more than 50 percent of VWs for 130 days post-detection until a vaccine is developed and deployed.

We also assume some of the other relevant countermeasure goals in the NBS Implementation Plan are successful. Specifically,

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[5] Haiqian Chen, Leiyu Shi, Yuyao Zhang, Xiaohan Wang, Jun Jiao, Manfei Yang, and Gang Sun, "Response to the COVID-19 Pandemic: Comparison of Strategies in Six Countries," *Frontiers in Public Health*, Vol. 9, September 2021; Jennifer Curtin, "The End of New Zealand's Zero-COVID Policy," *Think Global Health* blog, October 28, 2021; Emma E. Goldberg, Qianying Lin, Ethan O. Romero-Severson, and Ruian Ke, "Swift and Extensive Omicron Outbreak in China After Sudden Exit from 'Zero-COVID' Policy," *Nature Communications*, Vol. 14, No. 1, July 1, 2023.

[6] U.S. Department of Homeland Security, *Pandemic Influenza Preparedness, Response, and Recovery Guide for Critical Infrastructure and Key Resources*, September 19, 2006.

[7] White House, *National Biodefense Strategy and Implementation Plan: For Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health Security*, October 2022.

- Per Section 3.2 of the plan, pathogen-agnostic tests are available for thousands of samples on the first day and tens of thousands of samples per day within seven days.
- Pathogen-specific tests are available within 30 days, and rapid point-of-care tests are available within 90 days.[8]

We acknowledge that the 100 Days Mission is an ambitious goal and may not be achieved in practice; many pathogens have evaded effective vaccines for decades.[9]

We summarize these key assumptions in Table 3.2. Because our cross-scenario assumptions about the nature of the pathogens lean severe, the recommendations coming from this analysis will likely apply to less severe pathogen scenarios as well (although they may be overly protective for those scenarios). However, because our cross-scenario assumptions about human and organizational behavior are very optimistic, additional interventions beyond those discussed in this report may be necessary to protect against scenarios with imperfect human and organizational behavior.

Deterministic Analysis

In each scenario that we define, we set requirements using deterministic models. This approach allows us to avoid stochastic models that introduce additional complexity and reduce transparency and may lead to a false sense of precision given the large uncertainty in any input parameters we use.

TABLE 3.2
Key Assumptions for Pathogen Scenario Analysis

Response Component	Phenomenon	Assumption
Detection	Symptomatic surveillance	The disease is detected and recognized as a significant threat after the first death.
Human and organizational behavior	Governmental response	Government authorities implement a full response immediately once the threat is detected.
	VW behavior	VWs are absent from work only because of illness and death, not because of fear or caregiving responsibilities.
	Social distancing	Except for VWs, the public refrains from in-person contact outside their households. Essential activities are conducted through low-contact methods.
	PPE use	The use of PPE is enforced in all workplaces where VWs spend time.
	Compliance	There is full public compliance with the government response.
Pharmaceutical and diagnostic capabilities	Vaccine development	An effective vaccine is available to the entire U.S. population 130 days after detection.
	Diagnostic testing	Pathogen-agnostic tests are widely available within seven days, pathogen-specific tests within 30 days, and rapid point-of-care tests within 90 days.

[8] White House, 2022.

[9] Torresi et al., 2019.

CHAPTER 4

Scenario A: Fast

Chapter Summary

In this chapter, we introduce a scenario with a fast-spreading pathogen and explore possible physical defense strategies, numerical requirements for those strategies, and a worked example of how those requirements could be met: valveless elastomeric respirators and air decontamination tools. We then examine the existing state of the defenses discussed in the worked example and, finally, propose recommendations and policy options for how the U.S. government could develop, acquire, and test those defenses.

Overall Shape of Scenario

We imagine a rapidly spreading, airborne-transmissible novel pathogen that challenges the material availability and scale-up of physical countermeasures. Airborne transmission enables extremely rapid spread—as seen in measles, the most infectious known disease—and is also a transmission route that has historically not been widely recognized. Presymptomatic and asymptomatic transmission undercuts the efficacy of preventing spread by excluding infected individuals from indoor spaces, such as via self-isolation when experiencing symptoms, which further enables rapid spread. *Novelty* means that existing pathogen-specific countermeasures do not work against this pathogen. These characteristics, among others, contributed to the ability of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to cause global disruption.

We assume that the outbreak in this scenario is detected quickly and that the first death does not lag significantly behind the first disease case.

Modeling Default Outcomes

Given the immediate implementation of administrative controls and existing physical defenses, we assume that the growth rate of the Scenario A pathogen is similar to the early growth rate of SARS-CoV-2 in China's Hubei province (where SARS-CoV-2 first began spreading) after the initial strict lockdown of the city of Wuhan and other large cities in the province on January 23, 2020. The doubling time of the epidemic in Hubei during this period has previously been estimated at 3.43 days.

If a single person is infected at the start of the outbreak (analogous to an isolated domestic zoonotic pathogen spillover event), **more than 50 percent of VWs in the United States in this scenario are infected by day 79 after the first infection**, using simplistic assumptions about disease transmission. See Box 4.1 for calculation.

In certain adversarial scenarios that the United States might face, multiple originating infections could occur: for example, if bad actors intentionally infect numerous individuals simultaneously during an attack, which would cause the vital workforce to be compromised earlier.

BOX 4.1

Calculating Days Until VW Population Is Compromised

We define a very simple model using the epidemic doubling time to estimate the number of days until the VW population is compromised—when 50 percent of VWs are infected.

The number of doublings between initial pathogen introduction and this day is $n_d = \log_2(i_f/i_i)$, where i_f and i_i represent the final and initial cumulative incidences, respectively. If epidemic doubling time is t_d, the number of days from initial introduction to this day is $t = t_d * n_d = t_d * \log_2(i_f/i_i)$.

In this case, we are interested in the number of doublings from an initial introduction into the VW population until the final cumulative incidence in the VW population is 50 percent. To approximate the size of the VW population, we use the 2007 estimates by the National Infrastructure Advisory Council (NIAC). NIAC estimated around 17 million critical U.S. workers across three tiers in 2007; around 12 million of these were in the most-critical group.[a] Accounting for approximately 10-percent labor force growth since then, this scales up to about 19 million critical and about 14 million most-critical U.S. workers in 2025.[b] We use the average of the two growth-adjusted NIAC estimates, around 16 million, as the number of VWs in the United States. (The requirements we present can be easily adjusted if further studies pinpoint an updated estimate.)

Thus, $t = 3.43 * \log_2(50\,\%/(1/16{,}000{,}000)) = 79$ days.

This model does not account for changes in the doubling period as the epidemic progresses because of a decreasing number of susceptible people or spread to lower-density contact networks, but it is a useful approximation for our purposes here.

[a] National Infrastructure Advisory Council, *The Prioritization of Critical Infrastructure for a Pandemic Outbreak in the United States Working Group: Final Report and Recommendations by the Council*, U.S. Department of Homeland Security, January 16, 2007.

[b] Federal Reserve Bank of St. Louis, "Civilian Labor Force Level," webpage, last updated July 3, 2025.

Even with perfect administrative controls and a successful 100 Days Mission, as well as a relatively simple scenario with a single starting infection, too many VWs will be incapacitated. The timeline of pathogen spread is much faster than even the ambitious 100 Days Mission vaccine development timeline, and existing physical defenses, including air decontamination and available PPE, are insufficient to prevent this spread. Additional physical defenses are needed to prevent this outcome.

Potential Physical Defense Approaches

With pharmaceuticals and diagnostics initially unavailable and administrative controls quickly applied to their near-best case, there are three remaining defenses that can be used to help protect VWs from the Scenario A pathogen: PPE, elimination via source control, and engineering controls.

Personal Protective Equipment

Drawing on a previous analysis, we expect barrier PPE, which includes gloves, gowns, face shields, and goggles, to be abundant, easily improvised if needed, and effective at preventing respiratory droplets from landing in nonrespiratory mucosa, such as the eyes.[1] We therefore focus our analysis on respirators, which are

[1] Gryphon Scientific, 2024.

considerably less abundant or easy to improvise than barrier PPE. In Table 4.1, we summarize key features of four common categories of respirators.

Respirator efficacy is typically measured as a *protection factor* that reflects the fraction of particles in the ambient environment that penetrate or leak inside the unit. Protection factors are typically measured at the *most penetrating particle size* (MPPS) of the respirator's filter, although in most cases, protection is compromised more by leakage around a filter than by penetration through the filter. Although there are several ways to operationalize the protection factor metric,[2] we note two here:

- *simulated workplace protection factor* (SWPF), the protection factor while the respirator's wearer is simulating work activities
- *assigned protection factor* (APF), a number manually assigned by regulators, such as the Occupational Safety and Health Administration, to approximate the 5th-percentile workplace protection factor someone might achieve while wearing a certain category of respirator.

TABLE 4.1
Common Types of Respirators and Their Protection Factors Against the Most-Penetrating Particle Sizes

PPE Type	Filtering Facepiece Respirator (FFR)	Elastomeric Half-Mask Respirator (EHMR)	Elastomeric Full-Facepiece Respirator (EFFR)	Powered Air-Purifying Respirator (PAPR)
Example image				
APF[a]	10	10	50	• 25 (default) • 1,000 (if demonstrated by manufacturer)
Approximate mean SWPF range[b]	~100–1,000	~100–1,000	~1,000–10,000	• ~100–1,000 (loose-fitting facepiece) • ~10,000–100,000 (helmet or hood)
Source control (filtered exhalation)	Available on some models	Available on some models	Not commonly available	Not commonly available

SOURCES: From left to right: Alina Bitta/Adobe Stock; Oleksandr Dorokhov/Adobe Stock; Roman Milert/Adobe Stock; Thitiporn/Adobe Stock.
NOTE: Images are for illustration only; we do not endorse any specific products.
[a] Occupational Safety and Health Administration, *Assigned Protection Factors for the Revised Respiratory Protection Standard*, U.S. Department of Labor, OSHA 3352-02, 2009.
[b] T. J. Nelson, "The Assigned Protection Factor According to ANSI," *American Industrial Hygiene Journal*, Vol. 57, No. 8, August 1996.

[2] Personal Safety Division, *Key Considerations Regarding Respiratory Protection Assigned Protection Factors (APF)*, 3M, October 2019.

Negative-pressure respirators, such as FFRs (which include disposable N95 masks) or elastomeric respirators, usually require *fit testing* to lower the risk of ambient air leaking into the unit.[3]

Elimination via Source Control

If individuals infected with a Scenario A–like pathogen wear respirators, these devices may be able to perform *source control*, an elimination function, by reducing the number of infectious particles that they shed into the ambient space. Many types of respirators have unfiltered exhalation—for instance, respirators with exhalation valves or loose-fitting PAPRs—but negative-pressure models that provide two-way protection are available.[4] These models typically have the same filtration efficiency in both directions of airflow. Source control *efficacy* can be measured as the fraction of particles generated inside the respirator that penetrate or leak into the ambient environment (the reciprocal of which can be thought of as an "outward protection factor").[5] See Box 4.2.

Engineering Controls

The vital workforce may be further protected against a Scenario A–like pathogen through *engineering controls*, which involve removing the pathogen by decontaminating the indoor environment. Highly effective surface disinfectants are affordable, abundant, and easy to use, so we do not focus on them here.[6] Continuously decontaminating the air in occupied spaces poses a larger challenge because techniques for doing so have not yet been implemented widely.

Air decontamination interventions include ventilation and filtration systems that remove pathogens from the air and air disinfection systems that inactivate pathogens in ambient air. *Ventilation* involves a steady stream of outside air displacing indoor air. Many buildings in the United States have integrated heating, ventilation, and air conditioning (HVAC) systems and can achieve additional ventilation by opening windows.[7] Air filtration also is often built into HVAC systems.[8] Portable air filters can provide supplementary air filtration. Air disinfection tools include germicidal ultraviolet light (GUV) and germicidal vapors, such as propylene or triethylene glycol (which have a biophysical mechanism of action)[9] and low concentrations of hydrogen peroxide, hypochlorous acid, or hydroxyl radicals (which are oxidants), which could be used in occupied spaces during crises without posing an immediate severe health threat.[10] Air disinfection systems

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[3] National Institute for Occupational Safety and Health, "Fit Testing," webpage, February 3, 2025.

[4] "NIOSH Approves First Elastomeric Half Mask Respirator Without Exhalation Valve," *The Synergist*, January 2021.

[5] Xue Qi Koh, Anqi Sng, Jing Yee Chee, Anton Sadovoy, Ping Luo, and Dan Daniel, "Outward and Inward Protection Efficiencies of Different Mask Designs for Different Respiratory Activities," *Journal of Aerosol Science*, Vol. 160, February 2022.

[6] Environmental Protection Agency, "Selected EPA-Registered Disinfectants," webpage, last updated January 13, 2025a.

[7] Centers for Disease Control and Prevention, "Taking Steps for Cleaner Air for Respiratory Virus Prevention," webpage, March 1, 2024c.

[8] Masih Alavy and Jeffrey A. Siegel, "In-Situ Effectiveness of Residential HVAC Filters," *Indoor Air*, Vol. 30, No. 1, January 2020.

[9] Christine T. Styles, Jie Zhou, Katie E. Flight, Jonathan C. Brown, Charlotte Lewis, Xinyu Wang, Michael Vanden Oever, Thomas P. Peacock, Ziyin Wang, Rosie Millns, et al., "Propylene Glycol Inactivates Respiratory Viruses and Prevents Airborne Transmission," *EMBO Molecular Medicine*, Vol. 15, No. 12, December 7, 2023.

[10] Odessa Gomez, Kevin M. McCabe, Emma Biesiada, Blaire Volbers, Emily Kraus, Marina Nieto-Caballero, and Mark Hernandez, "Airborne Murine Coronavirus Response to Low Levels of Hypochlorous Acid, Hydrogen Peroxide and Glycol Vapors," *Aerosol Science and Technology*, Vol. 56, No. 11, 2022; Anais Paños-Crespo, Jorge Toledano-Serrabona, María Ángeles Sánchez-Garcés, and Cosme Gay-Escoda, "Evaluation of the Efficacy of Hydroxyl Radical ($OH^{\cdot}$) Release for Disinfection

BOX 4.2

Calculating the Required Combination of Personal Protective Equipment and Air Decontamination

We begin by defining a differential equation for the instantaneous rate of change of the number of airborne pathogens in a space (n) over time (t), assuming a well-mixed room:

$$\frac{d_n}{d_t} = \textit{rate of pathogens added} - \textit{rate of pathogens removed}.$$

Because the rate of pathogens removed from a room is dependent on the existing number of pathogens, we can rewrite this equation as

$$\frac{d_n}{d_t} = \frac{pIr}{P_o} - n\lambda,$$

where p is the number of people in a space, I is the fraction of those people who are infectious, r is the rate of airborne pathogen shedding by each infectious person in the space, P_o is the outward protection factor of the PPE worn by infectious people in the space, and λ is the sum total airborne pathogen inactivation and removal rate from all mechanisms, including

- natural decay (λ_n)
- ventilation (λ_v)
- settling (λ_s)
- air decontamination (λ_d).

To find the equilibrium number of pathogens in the room, we can set the rate of change to zero:

$$0 = \frac{pIr}{P_o} - n\lambda \rightarrow n = \frac{pIr}{P_o\lambda}.$$

The number of pathogens that the mean individual worker inhales in this room is

$$n_b = \frac{\textit{pathogens in volume of air inhaled}}{\textit{inward protection factor}} = \frac{\left(\frac{n}{v}\right)b\,t_w}{P_i} = \frac{pIrb\,t_w}{vP_iP_o\lambda},$$

where b is the individual's breathing rate, t_w is the amount of time the worker spends in the space, v is the volume of the space, and P_i is the inward protection factor of PPE worn by the worker.

To keep this number below a single infectious dose (x) inhaled,

$$x \geq \frac{pIrb\,t_w}{vP_iP_o\lambda} \rightarrow P_iP_o\lambda \geq \frac{pIrb\,t_w}{vx}.$$

We further simplify by setting $d = p/v$ as the volume density of people in the space.

The required combination of PPE and air decontamination is thus of the form

$$P_iP_o\lambda \geq \frac{dIrb\,t_w}{x}.$$

can also be designed into contained units that recirculate room air. These units can use air disinfection methods that would be unsafe if humans were exposed to them, such as high concentrations of ozone or other oxidants, as long as these methods remove those hazardous compounds before the disinfected air is released back into the room.

of the Air and Surfaces in the Dental Clinic: An *in Vitro* Study," *Medicina Oral, Patologia Oral, Cirugia Bucal*, Vol. 29, No. 1, January 1, 2024.

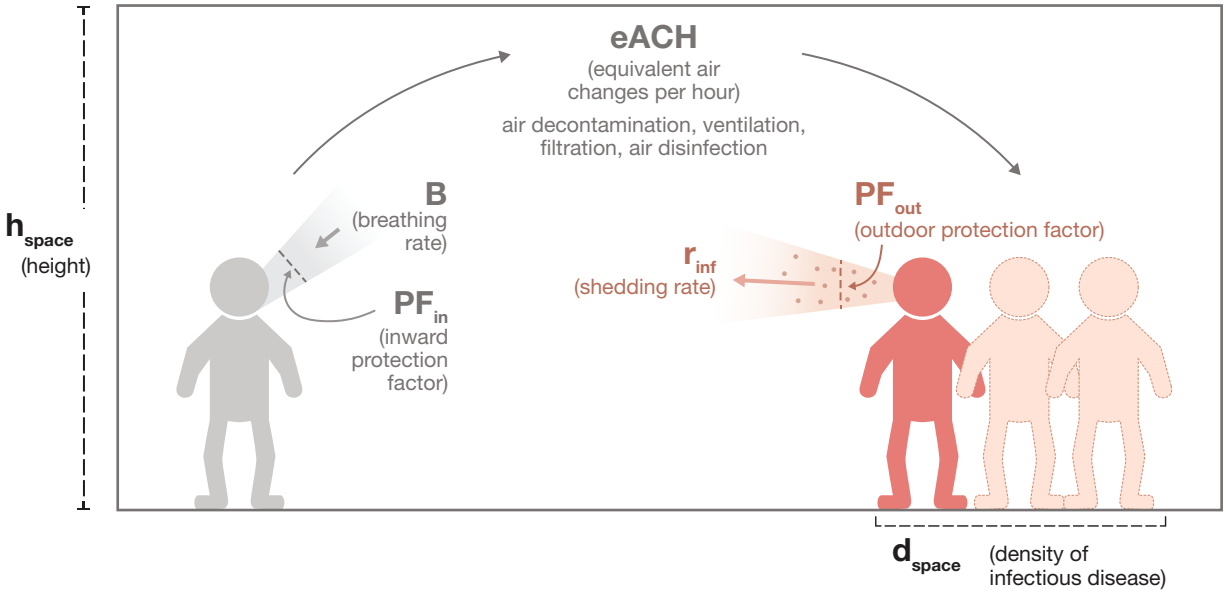
Air decontamination can be measured in equivalent air changes per hour (eACH). One eACH is equivalent to around 63.2 percent of the airborne pathogens in a room being removed or inactivated in one hour.[11] Two eACH is around 86.5 percent, and three eACH is around 95.0 percent.

Physical Defense Requirements

To estimate what combination of air decontamination and respirators might be needed to reduce infection risk, we use a modified Wells-Riley equation. Commonly used to make rapid, deterministic assessments of indoor aerosol transmission risk,[12] a *Wells-Riley model* assumes that pathogens build up to a steady concentration in a room. We believe that this model offers a useful framework for thinking about VW protection in this scenario. This approach allows us to quantify how combinations of respirators (both inward and outward protection) and air decontamination can affect the number of infectious doses that a VW inhales in an idealized setting.

Keeping with our assumption of near-perfect behavior, we assume VWs do not remove their PPE indoors; any eating, drinking, and sleeping occurs outdoors or in the private residences of VWs. We also assume that any settings where VWs may spend time are always at the same steady pathogen concentration (Figure 4.1).

FIGURE 4.1
Graphical Representation of the Wells-Riley Model Used to Set Air Decontamination and Respiratory Personal Protective Equipment Requirements



[11] Andrea Carlo D'Alicandro and Alessandro Mauro, "Air Change per Hour and Inlet Area: Effects on Ultrafine Particle Concentration and Thermal Comfort in an Operating Room," *Journal of Aerosol Science*, Vol. 171, June 2023.

[12] G. N. Sze To and C. Y. H. Chao, "Review and Comparison Between the Wells–Riley and Dose-Response Approaches to Risk Assessment of Infectious Respiratory Diseases," *Indoor Air*, Vol. 20, No. 1, February 2010.

Numerical Requirements

To determine how much protection is needed to help keep VWs safe, we define a plausible severe scenario and set rough values for key parameters. These parameters fall into two categories. *Pathogen-specific parameters* refer to the pathogen and its dynamics, including airborne shedding rate, infectious dose, and natural decay (Table 4.2). *Pathogen-independent parameters* are features of the world rather than the pathogen. The parameters used in this room-scale analysis might not match the population-scale doubling time analysis discussed earlier in this chapter; harmonizing them would be a much larger project outside the scope of this report. To emphasize that this analysis is very approximate, we round parameter values to the nearest order of magnitude where possible and appropriate.

The pathogen-independent parameters are

- volume density of people (d)
- fraction of infectious people (i)
- time worked in space with infectious people (t_w)
- breathing rate (b).

In the real world, each VW will require a different combination of these parameters because of the wide variety of work types and settings required for NCFs (e.g., dense factories, sensitive compartmented information facilities [SCIFs], biomedical laboratories).

We set a rough upper bound of ten for the product of these four parameters. With a typical breathing rate of 1 cubic meter per hour during light activity, this upper bound ensures that multiple types of high-risk VWs, such as the following, are included:

- emergency responders who spend 100 hours over the course of an outbreak in dense enclosed spaces with a high proportion of infectious people (one infectious person per ten cubic meters).
- hospital workers who spend 1,000 hours over the course of an outbreak in less dense spaces (one infectious person per 100 cubic meters).

TABLE 4.2
Pathogen-Specific Scenario A Parameters

Parameter	Value	Reference from Known Biology
Airborne shedding rate (r)	Infectious individuals emit an average of 10,000 viable pathogen units per hour during light activity (around 3 per second). We use plaque-forming units (PFU) and colony-forming units as measures of viable pathogen units.	One in 20 individuals infected with measles, the most infectious known pathogen, emit 11,000 infectious quanta per hour or more. This equates to 6,160 PFU using the approximate conversion factors of 0.8 quanta per $TCID_{50}$ and 0.7 $TCID_{50}$s per PFU.[a,b]
Infectious dose (x)	Exposure to one viable pathogen unit is enough to infect an individual.	The infectious dose for Q fever in aerosol is thought to be a single organism in up to 90 percent of cases.[c]
Natural decay rate (λ_n)	The pathogen has a natural decay rate of approximately zero per hour. The pathogen remains viable indefinitely until it is intentionally removed or inactivated.	Anthrax spores can persist for years in the environment,[d] although their decay rate in aerosols is unclear. (This decay rate is negligible compared with the other decay rates we will be considering, so we round to zero.)

[a] Alex Mikszewski, Luca Stabile, Giorgio Buonanno, and Lidia Morawska, "The Airborne Contagiousness of Respiratory Viruses: A Comparative Analysis and Implications for Mitigation," *Geoscience Frontiers*, Vol. 13, No. 6, November 2022.

[b] Centers for Disease Control and Prevention, "Measles Clinical Diagnosis Fact Sheet," webpage, May 19, 2025b.

[c] Rachael M. Jones, Mark Nicas, Alan E. Hubbard, and Arthur L. Reingold, "The Infectious Dose of *Coxiella burnetii* (Q Fever)," *Applied Biosafety*, Vol. 11, No. 1, March 2006.

[d] Zoë R. Barandongo, Amélie C. Dolfi, Spencer A. Bruce, Kristyna Rysava, Yen-Hua Huang, Hendrina Joel, Ayesha Hassim, Pauline L. Kamath, Henriette van Heerden, and Wendy C. Turner, "The Persistence of Time: The Lifespan of Bacillus Anthracis Spores in Environmental Reservoirs," *Research in Microbiology*, Vol. 174, No. 6, July–August 2023.

This bound of ten will also cover lower-risk VWs, such as workers in factories where initial countermeasure implementation can reduce the fraction of infectious people in the workplace to zero within days.

Taking into consideration the upper-bound setting and the pathogen-specific parameters, we calculate the minimum protection required to keep workers safe. Using the equation from Box 4.1 with these parameters, we find that the product of the following three factors must meet or exceed

$$P_i P_o \lambda \geq 100{,}000 \textit{ per hour},$$

where

- P_i represents the inward protection factor of the PPE worn by VWs.
- P_o represents the outward protection factor of the PPE worn by infectious people in the given space.
- λ represents the *air decontamination rate*, or how quickly pathogens are removed from the air through ventilation, filtration, or other means.

This result means that some combination of PPE and environmental air controls must reduce exposure by a factor of at least 100,000 per hour to achieve a sufficiently low infection risk in this high-risk scenario.

Worked Example Approaches: Respiratory Protection and Air Decontamination

To identify one achievable way to meet this requirement, we analyzed available types of respiratory protection and air decontamination methods.

Respiratory Protection

EHMRs are the most affordable means of providing respiratory protection when many days of protection are required.[13] According to a recent National Institute for Occupational Safety and Health (NIOSH) study, at least some models of EHMRs with N95-level filtration (and all tested models with P100-level filtration) appear to achieve a geometric mean inward SWPF of 200,[14] and thus also an arithmetic mean inward SWPF of 200 or higher per the arithmetic mean–geometry mean (AM-GM) inequality.[15] We assume that if the same design of EHMR were made without an exhalation valve, it would also achieve an outward protection factor of 200. At least some EHMR models achieve good fit on the first try for most wearers,[16] so there are solutions that could be scaled at the time of this writing, although fit testing every VW would be ideal. If every VW has one EHMR with filtered exhalation, protecting all VWs would require 16 million EHMRs with filtered exhalation using the estimate for the VW population from Box 4.1.

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[13] Gio Baracco, Sheri Eisert, Aaron Eagan, and Lewis Radonovich, "Comparative Cost of Stockpiling Various Types of Respiratory Protective Devices to Protect the Health Care Workforce During an Influenza Pandemic," *Disaster Medicine and Public Health Preparedness*, Vol. 9, No. 3, June 2015.

[14] Xinjian He, Evanly Vo, M. Horvatin, Y. Liu, M. Bergman, and Z. Zhuang, "Comparison of Simulated Workplace Protection Factors Offered by N95 and P100 Filtering Facepiece and Elastomeric Half-Mask Respirators Against Particles of 10 to 400 nm," *Journal of Nanotechnology and Materials Science*, Vol. 2, No. 2, September 7, 2015, Figure 1.

[15] D. J. H. Garling, "The AM–GM Inequality," *Inequalities: A Journey into Linear Analysis*, Cambridge University Press, 2007.

[16] Lisa A. Pompeii, Colleen S. Kraft, Erik A. Brownsword, Morgan A. Lane, Elisa Benavides, Janelle Rios, and Lewis J. Radonovich, Jr., "Training and Fit Testing of Health Care Personnel for Reusable Elastomeric Half-Mask Respirators Compared with Disposable N95 Respirators," *JAMA*, Vol. 323, No. 18, May 12, 2020.

Air Decontamination

With enough EHMRs with filtered exhalation, meeting the requirement would also require air decontamination strategies that could achieve at least 2.5 eACH in every vital workplace (100,000 per hour divided by [200 times 200]).

Multiple air decontamination strategies could achieve these air decontamination rates, such as filtration, ultraviolet (UV) light, glycols, or oxidant vapors, although we illustrate only portable air filters for simplicity. If the 16 million VWs worked in settings with an average ceiling height of 3 meters and a sparse occupant density of 100 square meters per person, there would be 4.8 billion cubic meters of space to protect. In one study by Dal Porto et al., a low-cost, makeshift portable air filter unit delivered around 1,200 cubic meters per hour of clean air at sub-micron particle sizes near the filter MPPS.[17] Protecting 4.8 billion cubic meters of space with 2.5 eACH would require 12 billion cubic meters of delivered clean air per hour, which would require 10 million portable air filter units similar to the one from Dal Porto et al.

Existing Personal Protective Equipment and Air Decontamination

We are not aware of any evidence that the United States has enough EHMRs with filtered exhalation to meet this requirement. To our knowledge, there were no major valveless EHMR models prior to 2020, although there are several models available now. The Strategic National Stockpile (SNS) piloted a program to procure and distribute EHMRs with filtered exhalation in 2021, although we are not aware of any large-scale stockpiling program for valveless EHMRs yet.[18] Existing stockpiles of valved EHMRs could also be modified to include exhalation filter adapters, and makeshift versions could be improvised.

We are also unaware of any evidence that the United States has enough portable air cleaners, although gradual adoption of higher indoor air quality standards, such as American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) 241,[19] may result in many indoor spaces achieving much higher air decontamination rates than they do at the time of this writing.

To ensure efficacy of these solutions, there must be testing and evaluation metrics to verify the functionality of individual components of the physical defense system (e.g., individual respirators or air decontamination units), as well as the system in the aggregate—especially logistical and compliance details that we have not considered in depth here.

Recommendations for Implementing Worked Example Approaches

One way to increase resilience to Scenario A would be for the U.S. government to implement the approaches discussed in this chapter. In the sections that follow, we offer notional high-level recommendations for U.S. government steps to implement these approaches. These recommendations should be considered only an initial attempt to describe one possible path forward, not the result of comprehensive analysis. They should be validated with more-detailed study before being acted on.

[17] Rachael Dal Porto, Monet N. Kunz, Theresa Pistochini, Richard L. Corsi, and Christopher D. Cappa, "Characterizing the Performance of a Do-It-Yourself (DIY) Box Fan Air Filter," *Aerosol Science and Technology*, Vol. 56, No. 6, 2022.

[18] Mihili Edirisooriya and Emily J. Haas, "Examining the Roles of Training, Fit Testing, and Safety Climate on User Confidence in Respiratory Protection: A Case Example with Reusable Respirators in Health Delivery Settings," *Sustainability*, Vol. 15, No. 17, 2023.

[19] ASHRAE, *ASHRAE Standard 241, Control of Infectious Aerosols*, 2023.

We lay out three sets of recommendations that the U.S. government could implement, depending on the time frame in which we might aim to achieve preparedness against Scenario A. For each time horizon, we detail recommendations pertaining to PPE, air decontamination, and testing and evaluation.

Short Term: Preparedness Within One Year

Primary Personal Protective Equipment Recommendation

Ensure access to at least enough EHMRs with filtered exhalation for the entire vital workforce. Ensuring access to enough of these EHMRs can be accomplished by a combination of multiple routes, including procuring and stockpiling valveless EHMRs, procuring exhalation filter adapters for existing stockpiles of EHMRs *with* exhalation valves, or even developing machines that could convert stockpiles of existing N95 FFRs into reusable EHMR-like products by adding an elastomeric face seal. For a rough cost estimate, we assume that because the United States likely does not have the manufacturing capacity to produce this much of either product in one year, unit costs will be significantly higher to compensate for rapid investments in manufacturing capacity. We therefore double the approximate unit costs of valveless EHMRs to $50 each, in which case direct procurement of 16 million units (using the estimate of the VW population from Box 4.1) would cost *$800 million*. This estimate does not include the costs of stockpile storage or of replacing expiring products in the stockpile. EHMR filters have typical shelf lives of two to five years, and facepieces around five to ten years, both depending on manufacturer instructions.[20]

Primary Air Decontamination Recommendation

Ensure access to sufficient air decontamination capacity in occupied vital workspaces. As discussed in the "Worked Example Approaches" section of this chapter, multiple air decontamination technologies could be used to achieve sufficient air change rates during crises, including germicidal UV light, germicidal vapors, and portable air filters. We use portable air filter procurement as a ballpark cost estimate. Using 10 million portable air filter units that cost $100 each (around 1.5 times higher than the cost of the roughly $70 unit described in Dal Porto et al., 2022), we calculate that direct procurement could cost $1 billion.[21]

Testing and Evaluation

We assume that no testing and evaluation are done for short-term preparedness.

Other Recommendations

- Develop a prioritized respirator and air decontamination distribution plan across VWs and vital workplaces. The subfunctions of NCFs most proximate to a threat response (i.e., the supply and distribution chain for respirators and air decontamination units) should receive protection first, because it would be impossible to protect the rest of the vital workforce without them.
- Develop and publish scalable respirator selection and evaluation apps to enable workers to select the respirators that likely fit them best and to demonstrate proper respirator usage.
- Stockpile fit testing materials, such as particle counter-based fit testing equipment, atomizers, and sweet or bitter agents, to ensure that VWs can achieve good fits on the respirators distributed to them.

[20] Lee A. Greenawald, Emily J. Haas, and Maryann M. D'Alessandro, "Elastomeric Half Mask Respirators: An Alternative to Disposable Respirators and a Solution to Shortages During Public Health Emergencies," *Journal of the International Society for Respiratory Protection*, Vol. 38, No. 2, 2021.

[21] Dal Porto et al., 2022.

Medium Term: Preparedness Within Three to Five Years

Primary Personal Protective Equipment Recommendation

This recommendation is the same as in the short term. However, we assume the EHMR costs are closer to existing bulk prices (as of this writing in 2025) because companies producing these products will not need to invest in as much manufacturing capacity (because the products can be procured over multiple years). If one valveless EHMR costs $25, direct procurement of 16 million units would cost $400 million.

Primary Air Decontamination Recommendation

This recommendation is the same as in the short term. Similar to the medium-term primary PPE recommendation, we assume that costs are closer to existing bulk costs because of lower manufacturing capacity needs. Using 10 million portable air filter units that are assumed to cost $50 each in bulk (around one-third cheaper than the individual unit in Dal Porto et al., 2022), we calculate that direct procurement could cost $500 million.[22]

Testing and Evaluation

We propose two levels of testing and evaluation: unit level and workplace level.

Unit-Level Testing

For respirators, we recommend **collecting a dataset of the simulated workplace and outward protection factors achieved** when different categories of PPE are issued to a random sample of workers who have never been trained on how to use this equipment.

For the air decontamination units, we recommend **collecting a dataset of the pathogen inactivation rates achieved** when different air decontamination devices or methods are set up by untrained workers in a controlled room with a fixed addition rate of a tracer pathogen. The workers should not be told the amount of each air decontamination tool they need for the space; they must be able to assess the required amount themselves from calculation instructions.

Workplace-Level Testing

To assess the ability of respiratory PPE and air decontamination units to work in combination with administrative controls, existing barrier PPE, and surface decontamination, we suggest **performing a workplace-level outbreak response to a common airborne respiratory infection**. We propose running this test in a cluster of U.S. Department of Defense (DoD) military installations that are relatively isolated from contact with the rest of the world, such as in training barracks. A subset of these installations should be *protected* with full administrative controls, PPE, and decontamination techniques, and rates of common airborne-transmissible respiratory pathogens, such as SARS-CoV-2, influenza, or respiratory syncytial virus (RSV) in both protected and unprotected installations should be regularly monitored.

If the measures in the protected cluster fail to successfully prevent the spread of a pathogen inside those military installations when the unprotected clusters also display outbreaks, the physical defenses must be reworked. (However, because seasonal respiratory viruses are much less transmissible than the pathogen in Scenario A, success at this test does not imply success against Scenario A, even though failure at this test implies failure against Scenario A.) We have not considered how such a study would be implemented in detail, so it is possible that legal, regulatory, or ethical considerations may constrain this test.

[22] Dal Porto et al., 2022.

Other Recommendations

- Assess the available stock of and surge manufacturing capacity for multiple air decontamination technologies and stockpile as much as necessary to meet demand.
- Purchase equipment to rapidly fit test 16 million VWs within one week.
- Develop a prioritized respirator and air decontamination distribution plan across VWs and vital workplaces. The NCFs most proximate to a threat response (i.e., the supply and distribution chain for respirators and air decontamination units) should receive protection first, because it would be impossible to protect the rest of the vital workforce without them.
- Evaluate emerging transmission-suppression tools, such as calcium salt nasal sprays for reducing exhaled aerosol counts and gel-based nasal sprays for increasing the number of pathogen units (e.g., individual virions or bacteria) in an infectious dose.[23]
- Evaluate and deploy methods for converting already stockpiled disposable N95 respirators into reusable elastomeric respirators.

Long Term: Preparedness Within Five to Ten Years

Primary Personal Protective Equipment Recommendation

This recommendation is the same as in the short and medium terms. Although our rough guess is that five to ten years would be enough time to invest in surge manufacturing capacity for respirators and air decontamination units, the best way to ensure that manufacturing capacity is reliable is to ensure a constant flow of purchases. Because the private market is unlikely to use the full surge capacity, these purchase orders would have to come from the U.S. government, so we assume the costs are the same as in the short- and medium-term cases.

Primary Air Decontamination Recommendation

This recommendation is the same as in the short and medium terms. As with the primary PPE recommendation, we assume costs are the same as in the short- and medium-term cases.

Testing and Evaluation

This would be the same as in the medium term.

Other Recommendations

- Invest in designing, prototyping, and testing innovative respirator products, such as ones that improve comfort, ergonomics, and ease of manufacturing or stockpiling, or ones that are UV light–compatible.
- Develop methods of sensing and reporting protection factors of worn respirators in real time.
- Investigate the feasibility of automating NCFs to reduce the number of workers who will need to work in person during a crisis.

[23] David Edwards, Anthony Hickey, Richard Batycky, Lester Griel, Michael Lipp, Wes Dehaan, Robert Clarke, David Hava, Jason Perry, Brendan Laurenzi, et al., "A New Natural Defense Against Airborne Pathogens," *QRB Discovery*, Vol. 1, July 7, 2020; John Joseph, Helna Mary Baby, Joselyn Rojas Quintero, Devin Kenney, Yohannes A. Mebratu, Eshant Bhatia, Purna Shah, Kabir Swain, Dongtak Lee, Shahdeep Kaur, et al., "Toward a Radically Simple Multi-Modal Nasal Spray for Preventing Respiratory Infections," *Advanced Materials*, Vol. 36, No. 46, November 2024.

Policy Options

Although the SNS did not stockpile EHMRs prior to the COVID-19 pandemic, it released a solicitation to procure EHMRs in 2021.[24] However, public-facing information about the SNS's contents does not indicate whether EHMRs are part of the existing stockpile. Therefore, the United States may not have the quantities of EHMRs and portable air filter units readily available to address Scenario A. The United States would need to invest in domestic manufacturing and stockpiling of EHMRs and air decontamination tools to protect all VWs. Policymakers may consider the following options to achieve a sufficiently large stockpile:

- **Partnerships between the federal government and private industry.** Leveraging existing programs, such as the National Institute for Standards and Technology's Manufacturing Extension Partnership, can connect the government with domestic manufacturers to meet federal procurement needs.[25] Expanding partnerships between private industry and federal agencies that fund domestic manufacturing of PPE, such as DoD and the U.S. Department of Health and Human Services, would also assist the United States in reaching these goals. PPE and air decontamination tools produced to meet the estimated requirements for Scenario A must be stockpiled to ensure that the federal government has these assets if needed. To do this, the United States could consider expanding the SNS or establishing a separate federal stockpiling initiative.
- **Expanding the SNS.** The Administration for Strategic Preparedness and Response houses the SNS, which is the country's federal stockpile of medical countermeasures (MCMs), including supplies and lifesaving devices.[26] The SNS is designed to augment states' needs during emergencies rather than serve as a sole supplier of MCMs for the U.S. public, and public-facing information about the SNS's products does not include the portable air filter units that are estimated to be necessary to protect VWs in Scenario A. As noted earlier, EHMRs were not part of SNS inventory prior to 2021, and EHMR stockpiling activities since are unclear based on public-facing information.[27] Therefore, the SNS's scope would need to be expanded to include these products. Additionally, legislative or executive directives would be required to reserve these MCMs for VWs. Existing SNS processes dictate that the federal government approves states' requests for SNS MCMs and distributes assets to states; however, states control the allocation and distribution of SNS MCMs within their respective jurisdictions.[28] Expansions of other federal stockpiles, such as those operated by DoD, the U.S. Department of Agriculture, and the U.S. Department of Veterans Affairs, could also be beneficial.[29] Although these stockpiles are designed for specific target populations, tapping into their resources may be necessary in an emergency, such as the one described in Scenario A.

[24] System for Award Management, "Elastromeric Half Mask Respirator—COVID-19," Notice ID 75A50121Q000111, U.S. General Services Administration, last updated April 1, 2021.

[25] Joseph R. Biden, Jr., *Ensuring the Future Is Made in All of America by All of America's Workers*, Executive Order 14005, January 25, 2021.

[26] Administration for Strategic Preparedness and Response, "Center for the Strategic National Stockpile," webpage, undated-a.

[27] System for Award Management, 2021.

[28] Administration for Strategic Preparedness and Response, "Requesting SNS Assets," webpage, undated-b.

[29] Animal and Plant Health Inspection Service, "National Veterinary Stockpile," webpage, U.S. Department of Agriculture, last updated March 30, 2024; Clifton G. Chappell, Roderick Gainer, and Kristin Guss, *Defense National Stockpile Center: America's Stockpile: An Organizational History, or An Organizational History of the Defense National Stockpile Center: America's National Stockpile*, Defense Logistics Agency, undated; U.S. Department of Veterans Affairs, "VHA Office of Emergency Management: Pharmaceutical Cache Program," webpage, last updated April 4, 2020.

- **Establishing a separate federal stockpiling initiative.** The SNS is meant to provide temporary support to states during a public health emergency, and the release of its assets is contingent on states submitting requests for support. States are then tasked with distributing MCMs within their respective jurisdictions.[30] Therefore, a new federal stockpiling mechanism might be needed to address the quantities of PPE and air decontamination tools necessitated by Scenario A, giving the federal government the flexibility to trigger deployment rather than waiting for state-level requests and granting increased decision-making authority about where assets go to address VW needs. However, creation of a separate stockpiling mechanism would likely require legislation or executive action, as well as dedicated resources, to manage and maintain the stockpile. Additionally, decisions would need to be made about which federal entity houses the stockpile. Furthermore, guidance as to who qualifies as a VW would need to be developed to ensure that deployed assets reach the target population.

The use of PPE to respond to biological threats will require rapid deployment and access, meaning that resilience should involve not only larger national stockpiles, such as the SNS, but also stockpiles at local levels. Considerable work has been done to note the importance of PPE stockpiling in high-risk facilities, specifically in health care settings. The COVID-19 pandemic and the 2014–2016 Ebola virus disease outbreak both exposed weaknesses in PPE stockpiling and public health supply chains, as well as underinvestment in public health preparedness and response. Hospitals that receive Medicare reimbursement from the Centers for Medicare and Medicaid Services (CMS) are required to follow regulations under the Emergency Preparedness Final Rule, which requires hospitals and medical facilities to develop and maintain an emergency preparedness program, inclusive of risk assessments and planning, training and testing, communication, and policies and procedures.[31] To create resilient stockpiles at local levels, the United States could do the following:

- **Revise and expand the CMS Emergency Preparedness Final Rule.** Although this rule is not specific to biological threats, this rule could be revised, similar to changes in 2019, to require health care facilities to maintain 100 days of respiratory protection. Scenario A points to a critical need for PPE supplies and subsequent stockpiles; however, the COVID-19 pandemic highlighted stockpile vulnerabilities and a time lag between SNS requests and frontline access, pointing to a need for requirements to be set in place. Expansion of the Emergency Preparedness Final Rule, including a requirement for 100-day respiratory PPE stockpiles and corresponding training for staff, would ensure that adequate supplies and competencies are maintained to respond to such a biological event.[32]

We have not performed a thorough analysis of previous policy proposals or recommendations, but many of these policy options have been proposed in different forms before. We do not claim that these policy options are fully novel insights from this analysis.

[30] Administration for Strategic Preparedness and Response, undated-b.

[31] Centers for Medicare and Medicaid Services, "Emergency Preparedness Rule," webpage, last updated December 30, 2024c.

[32] Centers for Medicare and Medicaid Services, 2024c.

CHAPTER 5

Scenario B: Silent

Chapter Summary

In this chapter, we introduce a pathogen that is similar to the Scenario A pathogen, but it has the added ability to spread undetected for multiple months. As in Chapter 4, we first describe the characteristics of this pathogen and how its epidemiology differs from Scenario A. Next, we explore possible physical defense strategies in the scenario, as well as numerical requirements for those strategies and worked examples of how those requirements could be met: pathogen-agnostic early warning systems that use long-read metagenomic sequencing (MGS) of nasal swabs or short-read MGS of airplane wastewater. We then examine the existing state of the defenses discussed in the worked example and finally propose recommendations for how the U.S. government could develop, acquire, and test those defenses.

Overall Shape of Scenario

Scenario B involves an extension of Scenario A to additionally challenge *detection*. As in Scenario A, we imagine a rapidly spreading, airborne-transmissible pathogen, but it has extensive presymptomatic spread.

Presymptomatic spread undercuts the efficacy of symptomatic surveillance at detecting the disease. Traditional symptomatic surveillance relies on astute physicians or epidemiologists to identify unusual patterns of symptoms or infections.[1] If the disease spreads significantly before any infected individuals develop symptoms, even the most discerning clinicians might fail to detect the outbreak via symptomatic surveillance until the disease has already infected a large number of people. This dynamic occurred with the human immunodeficiency virus (HIV), which spread without being identified from 1959 (if not earlier)[2] until the first official reporting of an unusual cluster of immune deficiencies in Los Angeles in 1981.[3] Scenario B could occur even if mild and nonspecific symptoms are present while people are infectious because symptoms may be regarded as a seasonal cold.

Pathogen novelty, as in Scenario A, undercuts the efficacy of most existing molecular diagnostics. Multipathogen panels, such as the BioFire respiratory panel that detects 22 common respiratory pathogens, are typically based on polymerase chain reaction (PCR) and will likely detect only novel pathogens that are very

[1] Kenneth D. Mandl, J. Marc Overhage, Michael M. Wagner, William B. Lober, Paola Sebastiani, Farzad Mostashari, Julie A. Pavlin, Per H. Gesteland, Tracee Treadwell, Eileen Koski, et al., "Implementing Syndromic Surveillance: A Practical Guide Informed by the Early Experience," *Journal of the American Medical Informatics Association*, Vol. 11, No. 2, March–April 2004.

[2] Michael Worobey, Marlea Gemmel, Dirk E. Teuwen, Tamara Haselkorn, Kevin Kunstman, Michael Bunce, Jean-Jacques Muyembe, Jean-Marie M. Kabongo, Raphaël M. Kalengayi, Eric Van Marck, M. Thomas P. Gilbert, and Steven M. Wolinsky, "Direct Evidence of Extensive Diversity of HIV-1 in Kinshasa by 1960," *Nature*, October 2, 2008.

[3] HIV.gov, "A Timeline of HIV and AIDS," webpage, undated.

similar to ones they test for.[4] For example, the BioFire respiratory panel has two pan-influenza targets that might theoretically detect novel viruses in the influenza A genus, but the panel likely would be unable to detect novel pathogens outside this genus.[5] Pathogens within this genus could possibly also be engineered to avoid detection by the panel. Diagnostics that use such gene editing tools as clustered regularly interspaced short palindromic repeats, better known as CRISPR,[6] are another method that could test for many pathogens simultaneously (and were the subject of a recent Defense Advanced Research Projects Agency [DARPA] program),[7] but these diagnostics are also limited to specific sequences enumerated in advance. Diagnostic methods that rely on large libraries of primers or probes may be able to detect novel pathogens that share similar sequence segments with known pathogens used in constructing the library, but such diagnostics may be unable to detect pathogens that have sufficiently different sequences or are engineered to avoid known probe sequences. For example, hybridization capture sequencing tools, such as VirCapSeq-VERT, can detect only pathogens that have sections with over 60-percent sequence homology to the pathogens used to generate the tool's probe library.[8] Sarbecoviruses show around 50-percent sequence similarities with other coronaviruses, so SARS-CoV-1 (the first discovered sarbecovirus)[9] might not have been detected by any of these tools if they had existed at the time of its initial emergence in 2002.

Because pathogen genomes come in multiple forms—for instance, double-stranded versus single-stranded DNA (deoxyribonucleic acid) or RNA (ribonucleic acid)—additional preparation steps are generally needed to convert the genetic material into a form compatible with the molecular diagnostic (typically, double-stranded DNA).[10] If these steps are not completed for each form of pathogen genome, the molecular diagnostic may fail to detect entire categories of pathogens. Additional data analysis steps might also be necessary for positive-sense versus negative-sense RNA.

Modeling Default Outcomes

Until the pathogen is detected, no administrative, physical, or pharmaceutical interventions are implemented, so we assume that the pathogen will instead have a growth rate approaching an *uncontrolled* highly transmissible airborne disease in a naive population, such as SARS-CoV-2 in China after the end of its restrictive zero-COVID policies in December 2022. During this period, SARS-CoV-2 appeared to have a doubling time of 1.6 days (although this number might have been influenced by changes in case-reporting practices during the studied period).[11] Notably, this doubling time is almost twice as fast as the doubling time we considered in Scenario A, because the outbreak in Scenario A was quickly detected and administrative controls were applied to slow the pathogen spread.

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[4] bioMérieux, "BIOFIRE® Respiratory 2.1 (RP2.1) Panel," webpage, undated.

[5] bioMérieux, undated.

[6] Catherine A. Freije and Pardis C. Sabeti, "Detect and Destroy: CRISPR-Based Technologies for the Response Against Viruses," *Call Host and Microbe*, Vol. 29, No. 5, May 2021.

[7] Defense Advanced Research Projects Agency, "DIGET: Detect It with Gene Editing Technologies," webpage, undated.

[8] Thomas Briese, Amit Kapoor, Nischay Mishra, Komal Jain, Arvind Kumar, Omar J. Jabado, and W. Ian Lipkin, "Virome Capture Sequencing Enables Sensitive Viral Diagnosis and Comprehensive Virome Analysis," *mBio*, Vol. 6, No. 5, October 2015.

[9] Zigui Chen, Siaw S. Boon, Maggie H. Wang, Renee W. Y. Chan, and Paul K. S. Chan, "Genomic and Evolutionary Comparison Between SARS-CoV-2 and Other Human Coronaviruses," *Journal of Virological Methods*, Vol. 289, March 2021.

[10] Nimrat Khehra, Inderbir S. Padda, and Cathi J. Swift, *Polymerase Chain Reaction (PCR)*, StatPearls Publishing, 2025.

[11] Goldberg et al., 2023.

We are uncertain whether it is biologically possible for such a rapid doubling time to occur without any infected individual displaying symptoms. However, we are not yet aware of any reason a pathogen with these characteristics would be theoretically *impossible*, and because we are not limiting our analysis to known pathogens (or even those that may be plausible to engineer in the short term), we choose to use this rapid doubling time for this analysis to provide a reasonable safety margin for the scenario category.

Because there are no administrative controls, VWs are not systematically likely to get infected any sooner or later than the rest of the population; they are mixed into the general population. We believe that this is a reasonable assumption because the VW population includes a variety of occupations at widely varying levels of required workplace contact with others. To calculate the day on which more than 50 percent of VWs would be infected absent intervention, we can use the same equation derived in Chapter 4, now with a single infection in the general population used in the denominator:

$$t = t_d * \log_2\left(\frac{i_f}{i_i}\right) = 1.6 * \log_2\left(50\% / \frac{1}{340{,}000{,}000}\right) = 44 \text{ days.}$$

More than 50 percent of VWs are infected by day 44 after the first infection. To maintain the challenge to symptomatic surveillance, we assume that nobody infected with the pathogen displays symptoms for months or years after initial infection; symptom delays are seen in the longer end of the distribution of the incubation period of primary tuberculosis,[12] and, more famously, acquired immunodeficiency syndrome (AIDS)[13] (although nonspecific flu-like symptoms of acute HIV infection typically occur within four weeks of exposure to the virus).

Potential Physical Defense Approaches

One possible approach to defending against Scenario B is to use preemptive countermeasures to stifle pathogen transmission before we are even aware of an outbreak, such as air decontamination and PPE, as per the requirements from Scenario A. However, without strict administrative controls (which are unlikely to be applied in the absence of a visible symptom-causing threat), there might still be many infections occurring from direct or close-range contact between people, no matter how effective air decontamination and PPE are. Although this approach may work in mild scenarios, it might not be reliable in the worst cases.

A second approach is to build an early detection system that can detect the pathogen before too many VWs get exposed, enabling the swift imposition of administrative controls and the countermeasures described in Scenario A that can halt further spread. Because of the pathogen's novelty, such an early detection system would need to be *pathogen-agnostic*: able to detect previously unknown pathogens, even with very large sequence deviations from known pathogens.

This system does *not* need to diagnose individuals or locate specific infections; it merely needs to serve as a potential trigger for proactive, universal implementation of the administrative controls and physical defenses described in Scenario A. Because a pathogen-agnostic detection system is not intended to contain an outbreak geographically, it can operate with a much less stringent detection threshold than systems intended to detect outbreaks early enough for geographic containment. This allows for a much sparser deployment of these detection systems. Pathogen-agnostic systems can be paired with a thorough threat characterization

[12] Marcel A. Behr, Paul H. Edelstein, and Lalita Ramakrishnan, "Revisiting the Timetable of Tuberculosis," *BMJ*, Vol. 362, August 2018.

[13] Victoria State Government Department of Health, "Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS)," webpage, last updated April 9, 2025.

pipeline that can help sort out false alarms and ensure that the systems' results are credibly triggering costly response actions.

Early detection systems have the following three basic components:

1. **Sample types and collection sites.** Possible sample types include respiratory tract samples (e.g., nasal swabs or saliva samples from clinical visits or volunteers), wastewater samples (e.g., from municipal sewage or airport triturators that grind waste from airplanes), blood samples (e.g., from blood banks or serum banks), and air samples (e.g., from air filters or aerosol impingers), among others.
2. **Sample processing pipeline.** The most-mature technology of which we are aware that can detect arbitrary unknown pathogens is untargeted metagenomic next-generation sequencing (mNGS), which can sequence both known and unknown nucleic acid fragments in a sample rather than only targeting known sequences.[14] For this reason, others have proposed mNGS-based pathogen early detection systems.[15] mNGS sequencers are not uncommon; the company with the largest market share has sold over 20,000 such devices.[16] (mNGS is also used in the hybridization capture sequencing methods that we earlier deemed might fail to detect the pathogen, such as VirCapSeq-VERT, but those methods introduce a step before mNGS that limits the pathogen-agnosticism of the system.) Other technologies could eventually be used for sample processing, such as protein sequencing or mass spectrometry, but we do not explore them in depth here because they are not yet widely available in a form that could be used to detect novel pathogens.[17] These technologies could enable detection of threats not based on standard nucleic acids, such as prions, which we do not discuss here. As with the other molecular diagnostics mentioned in the previous section, preparation steps are required to ensure that all pathogen genomes are converted into a form readable by the sequencer being used (generally double-stranded DNA, although nanopore sequencers can sequence some RNA directly).[18]
3. **Detection algorithm for identifying anomalies.** The ideal early detection algorithm for novel pathogens would detect any segment of a nucleic acid sequence that does not map to a known pathogen and has not appeared before in the (large) fraction of reads from baseline background sources. (Non-novel pathogen outbreaks can be detected using existing algorithms that match sequenced reads to known pathogen sequences.) If a previously unseen sequence segment begins to appear many times, further

[14] Wei Gu, Xianding Deng, Marco Lee, Yasemin D. Sucu, Shaun Arevalo, Doug Stryke, Scot Federman, Allan Gopez, Kevin Reyes, Kelsey Zorn, et al., "Rapid Pathogen Detection by Metagenomic Next-Generation Sequencing of Infected Body Fluids," *Nature Medicine*, Vol. 27, No. 1, January 2021.

[15] Rhys Dubin, Rassin Lababidi, John Moulton, Harshini Mukundan, Lillian Parr, Christine Parthemore, Saskia Popescu, and Daniel P. Regan, *Pathogen Early Warning: A Progress Report and Path Forward*, ed. by Francesco Femia, Janne E. Nolan Center on Strategic Weapons, Council on Strategic Risks, December 2022; Karrie K. K. Ko, Kern Rei Chng, and Niranjan Nagarajan, "Metagenomics-Enabled Microbial Surveillance," *Nature Microbiology*, Vol. 7, No. 4, April 2022; Chelsea Liang, James Wagstaff, Noga Aharony, Virginia Schmit, and David Manheim, "Managing the Transition to Widespread Metagenomic Monitoring: Policy Considerations for Future Biosurveillance," *Health Security*, Vol. 21, No. 1, January–February 2023; Siddhanth Sharma, Jaspreet Pannu, Sam Chorlton, Jacob L. Swett, and David J. Ecker, "Threat Net: A Metagenomic Surveillance Network for Biothreat Detection and Early Warning," *Health Security*, Vol. 21, No. 5, September–October 2023.

[16] Illumina, "Illumina Underscores Commitment to Shareholder Value and Responds to Carl Icahn's Statements," press release, March 20, 2023.

[17] Javier Antonio Alfaro, Peggy Bohländer, Mingjie Dai, Mike Filius, Cecil J. Howard, Xander F. van Kooten, Shilo Ohayon, Adam Pomorski, Sonja Schmid, Aleksei Aksimentiev, et al., "The Emerging Landscape of Single-Molecule Protein Sequencing Technologies," *Nature Methods*, Vol. 18, No. 6, June 2021.

[18] Charlotte Soneson, Yao Yao, Anna Bratus-Neuenschwander, Andrea Patrignani, Mark D. Robinson, and Shobbir Hussain, "A Comprehensive Examination of Nanopore Native RNA Sequencing for Characterization of Complex Transcriptomes," *Nature Communications*, Vol. 10, No. 1, July 31, 2019.

investigation into its origins and potential pathogenicity is likely warranted, especially if it appears in multiple sample types, grows in abundance over time, or contains markers of genetic engineering. Sequencing errors often create the appearance of novel sequence segments, but random errors would be unlikely to produce novel segments that appear multiple days in a row.[19] The exact threshold number of observations at which a novel segment should be flagged for detection will depend on the system's tolerance for false alarms and capacity to further investigate detected anomalies, which we will not analyze here. Higher detection thresholds will increase the risk of false negatives (where additional sampling and sequencing may be needed to detect the pathogen in time), and lower detection thresholds will increase the risk of false positives.

We focus on anomaly detection here, and we do not discuss follow-on investigation or threat characterization steps that would likely be required to understand the threat before making any decisions to implement costly countermeasures. An anomaly detection system alone will not indicate likely disease severity, especially for novel pathogens without visible symptoms.

Physical Defense Requirements

A metagenomic early detection system can help protect NCFs in this scenario. As in Scenario A, we now derive an equation to estimate order-of-magnitude system requirements (see Box 5.1). We work backward from the *detection threshold* (o_t), the number of times a particular pathogen genome segment must be observed on the day of detection for the pathogen to be flagged.

Because administrative and physical countermeasures will not be applied until cumulative incidence approaches 50 percent, and because easy ways to determine infection status (e.g., symptoms or diagnostics) would not be initially available to most people, additional administrative countermeasures beyond those described in Chapter 4, such as wearing PPE at home and sleeping in separate rooms, might be needed to prevent spread to VWs within households, not just within workplaces.

Numerical Requirements

Under our starting assumption of full implementation of controls immediately post-detection, the bare minimum requirement to meet the goal of preserving NCFs is to detect the pathogen before 50 percent of VWs (and thus 50 percent of the general population) are infected with it. However, because it will take time to distribute PPE and air decontamination equipment to vital workplaces, even with excellent organizational behavior, we aim for the early detection system to detect the pathogen one week before 50 percent of VWs are infected in the mean case. For detecting one week before 50 percent of VWs are infected, the cumulative incidence at detection can be back-calculated using the pathogen doubling time of 1.6 days. One week is 7/1.6 = 4.375 doublings, and 4.375 doublings before 50-percent cumulative incidence is around 2.4 percent cumulative incidence. To carry forward the spirit of the order-of-magnitude estimations from Scenario A, we set the requirement at detection before 1-percent cumulative incidence.

We assume that 100 observations of a particular sequence segment of length 100 are required for detection, similar to the mean order-of-magnitude assumption made in Grimm et al., 2024.[20] We further assume

[19] Nucleic Acid Observatory Consortium, "A Global Nucleic Acid Observatory for Biodefense and Planetary Health," arXiv, arXiv:2108.02678, August 5, 2021.

[20] Simon L. Grimm, Jeff T. Kaufman, Daniel P. Rice, Charles Whittaker, William J. Bradshaw, and Michael R. McLaren, "Inferring the Sensitivity of Wastewater Metagenomic Sequencing for Virus Detection and Monitoring," Version 3, medRxiv, October 8, 2024.

BOX 5.1

Estimating the Detection Threshold for a Metagenomic Early Detection System

The expected number of daily observations of a particular pathogen genome segment in a system is the fraction of all sequencing reads containing that segment multiplied by the total number of reads taken daily, so

$$o_t \leq I_s a f n_r,$$

where I_s is the incidence of the pathogen in the sampled population on the day of sampling. Because there is a time delay (τ) between sample collection and the completion of sample processing, $I_s = \frac{I_d}{2^{\frac{\tau}{t_d}}} = I_d 2^{-\tau/t_d}$ if I_d is the required incidence on the day of detection. For this order-of-magnitude analysis, we assume that incidence is approximately equal to cumulative incidence on the day of detection, because a doubling time of 1.6 days would mean that, at any given time in the early stages of an outbreak, most people who have ever been infected with the pathogen are currently shedding.

For human bodily fluid samples, such as nasal swabs, a is the relative abundance of the pathogen genome in samples from infectious people. For environmental samples, such as wastewater, a is the relative abundance of the pathogen if 100 percent of people in the sample catchment were infected.[a]

f is the fraction of all reads from the pathogen that contain a particular segment. For simplicity, we assume that if the pathogen genome length is g, there are g possible pathogen reads assuming a circular pathogen genome. (This calculation technically varies for different sequencing methods, and the number of possible pathogen reads per genome may vary because not all reads are a constant length, but for the purposes of this rough estimation, this assumption will not change results significantly.) Assuming, for simplicity, that the sequencing read length is a constant l, the segment length is k, and sequencing reads are not biased toward some segments over others, the number of possible pathogen reads containing the segment is $l - k + 1$, so $f = \frac{(l - k + 1)}{g}$.

n_r is the total daily number of pathogen reads taken from all samples.

In expanded form, the detection requirement is expressed as

$$o_t \leq \frac{a n_r I_d 2^{-\frac{\tau}{t_d}} (l - k + 1)}{g}.$$

This requirement assumes that incidence in the sampled population either matches or leads incidence in the general population, which is a reasonable assumption when sampling is in large volumes (e.g., when sampling covers more than 1,000 unique individuals per day) and geographically widespread.

[a] Grimm et al., 2024.

that the pathogen has a genome of 30,000 base pairs, similar to that of SARS-CoV-2.[21] Because increasing the genome length also results in an increased relative abundance of reads from the pathogen in samples (given a constant concentration of genome copies in each sample, and all else equal), we use relative abundance and genome length numbers for SARS-CoV-2 and assume that their ratio remains constant for pathogens with both longer and shorter genome lengths. We further assume that the relative abundance of the Scenario B pathogen matches the relative abundance of SARS-CoV-2 in all sample types. This might be an optimistic

[21] Changchang Cao, Zhaokui Cai, Xia Xiao, Jian Rao, Juan Chen, Naijing Hu, Minnan Yang, Xiaorui Xing, Yongle Wang, Manman Li, et al., "The Architecture of the SARS-CoV-2 RNA Genome Inside Virion," *Nature Communications*, Vol. 12, No. 1, June 24, 2021.

estimate for wastewater samples because SARS-CoV-2 appears to shed more in wastewater than other respiratory viruses,[22] although because the Scenario B pathogen may be shed in similar quantities as SARS-CoV-2, its relative abundance may be similar to SARS-CoV-2 in wastewater.

The requirement thus becomes

$$300{,}000{,}000 \leq an_r 2^{-\frac{\tau}{1.5}}(l - 101).$$

Worked Example Approach: Pathogen-Agnostic Early Detection System

We examine two possible systems for meeting this requirement, although many more might be feasible: a system that uses long-read sequencing of nasal swabs and a system that uses short-read sequencing of wastewater samples. These two sample types will capture such respiratory pathogens as the Scenario B pathogen: nasal swabs directly from the respiratory tract, wastewater partially from swallowed respiratory secretions, and any enteric pathogen replication.[23] However, these systems might not capture pathogens that do not spread via the respiratory tract, such as primarily blood-borne or sexually transmitted diseases. Additional sample types would be necessary to capture those pathogens.

Long-Read Sequencing of Nasal Swabs

Nasal swabs can be collected from random volunteers, such as people visiting clinics for other reasons, volunteers in busy public places, or a corps of regularly swabbed volunteers, or they can be acquired from leftovers of laboratory diagnostics. We assume that 10,000 nasal swabs are taken per day from a geographically distributed population, so incidence in the sample catchment is likely to match incidence in the general population, although it is possible that the incidence in the sample catchment lags behind incidence in the general population in some scenarios. These nasal swabs are pooled and sequenced by a long-read sequencer, such as the PromethION,[24] one of the highest-throughput long-read sequencers available on the market. (It is worth noting that sequencing error rates on the PromethION and similar long-read nanopore sequencers may still be too high to enable distinguishing between outbreaks of novel variants and known variants of existing pathogens, even though overall anomaly detection is feasible with these long-read sequencers.)

We assume samples are collected daily, and the pipeline of sample collection, prep, sequencing, and data analysis takes 1 day in total, so $\tau = 1$ day. PromethION flow cells appear to read an average of around 3 billion bases in 12 hours,[25] leaving another 12 hours for sample collection, prep, and data analysis. Nanopore sequencers can read sequences up to millions of bases long,[26] but we assume read lengths from nasal swabs average around 1,000 base pairs, roughly matching data observed from the Nucleic Acid Observatory.[27] With an average read length of 1,000 and 3 billion bases read in 12 hours, a single flow cell might thus sequence 3 million reads in 12 hours. We assume that reads from the pathogen are also around 1,000 base pairs.

[22] Simon Grimm, Dan Rice, and Mike McLaren, "Estimating the Sensitivity of Wastewater Metagenomic Sequencing Using Nasal Swabs," Nucleic Acid Observatory, June 8, 2025.

[23] Michael D. Parkins, Bonita E. Lee, Nicole Acosta, Maria Bautista, Casey R. J. Hubert, Steve E. Hrudey, Kevin Frankowski, and Xiao-Li Pang, "Wastewater-Based Surveillance as a Tool for Public Health Action: SARS-CoV-2 and Beyond," *Clinical Microbiology Reviews*, Vol. 37, No. 1, March 14, 2024.

[24] Oxford Nanopore Technologies, "PromethION," webpage, undated-b.

[25] Simon Grimm, "ONT Swab Sequencing Statistics," *Simon's Public NAO Notebook* blog, June 20, 2025.

[26] Oxford Nanopore Technologies, "PromethION [PromethION 24 and PromethION 48]," webpage, undated-c.

[27] Grimm, 2025.

In nasal swabs, we estimate that the relative abundance of SARS-CoV-2 in a nasal swab from an infected individual is 10^{-3}, using the order of magnitude observed in initial data collected by the Nucleic Acid Observatory and the rough mode of past studies compiled by the same group.[28]

To meet the requirement, the daily number of reads that must be sequenced in this system is thus

$$\frac{300{,}000{,}000}{10^{-3} * 2^{\frac{1}{126}}(1{,}000 - 101)} \leq n_r, \text{ or } n_r \geq 514{,}643{,}000 \text{ (approximately 515 million).}$$

Dividing the 515 million daily reads required by the 3 million reads that a single flow cell may be able to read in 12 hours, 172 flow cells must be run per day. These 172 flow cells could each be assigned to a different geographic region of the country (and thus a different subset of the 10,000 daily nasal swabs), but they do not necessarily need to be. Arrangements in which multiple flow cells all cover the same region of the country are possible, as long as the required number of daily reads are taken from the nasal swab pool.

Short-Read Sequencing of Wastewater Samples

For this system, we assume that one wastewater sample is collected daily from triturators (airplane waste-grinding machines) at ten major international airports, which enables a large geographic sample coverage. These wastewater samples are sequenced by a high-throughput short-read sequencer, such as the NovaSeqX.[29] (The Nucleic Acid Observatory has noted that long-read sequencing on wastewater samples is unhelpful because recoverable nucleic acid fragments from wastewater tend to be short, so we do not consider long-read sequencing of wastewater here.[30])

We further assume that the pipeline of sample collection, prep, sequencing, and data analysis takes 2 days in total, so $\tau = 2$ days. Per discussion with Nucleic Acid Observatory staff, we estimate that, in practice, a NovaSeq X 10B flow cell might sequence 8 billion reads with an average length of 180 base pairs in one day, leaving 24 hours for sample collection, prep, and data analysis.

We estimate that the relative abundance of *intact* pathogen nucleic acids in airplane wastewater is 10^{-6} at 1-percent incidence or 10^{-4} at 100-percent incidence using the rough mode of the municipal wastewater studies compiled by the Nucleic Acid Observatory (although airplane wastewater likely has higher pathogen relative abundance than municipal wastewater, per discussion with Nucleic Acid Observatory staff).[31] Nucleic acids in wastewater are commonly degraded, but we only consider the relative abundance of fragments that are sufficiently intact to be read by a sequencer.[32]

To meet the requirement, the daily number of reads that must be sequenced in this system is thus

$$\frac{300{,}000{,}000}{10^{-4} * 2^{\frac{2}{126}}(180 - 101)} \leq n_r, \text{ or } n_r \geq 90{,}319{,}527{,}721 \text{(approximately 90 billion).}$$

If one 10B flow cell can sequence 8 billion reads per day, 12 10B flow cells are needed daily to sequence 90 billion reads.

Although incidence in airplane waste may be a leading indicator of incidence in the general U.S. population in scenarios in which the outbreak begins outside the United States and enters the country via air travel,

[28] Grimm, Rice, and McLaren, 2025; Simon Grimm and Will Bradshaw, "Investigating the Sensitivity of Pooled Swab Sampling for Pathogen Early Detection," Nucleic Acid Observatory, July 1, 2024, footnote 2.

[29] Illumina, "NovaSeq X Series," webpage, undated-a.

[30] SecureBio, "Sampling and Sequencing Simulator," webpage, undated.

[31] Grimm et al., 2024.

[32] Mengyang Zhang, Laura Roldan-Hernandez, and Alexandria Boehm, "Persistence of Human Respiratory Viral RNA in Wastewater-Settled Solids," *Applied and Environmental Microbiology*, Vol. 90, No. 4, April 2024.

it might otherwise lag incidence in the U.S. population. Beyond capturing different pathogen types, this is another reason we propose a layered system involving both airplane wastewater (capturing travelers) *and* nasal swabs (more closely capturing the general U.S. population).

Existing Biosurveillance Capacity

Progress toward such systems is already being made on two fronts: (1) developing large-scale sampling and data analysis infrastructure (even if the sample processing and detection algorithms are not appropriate for pathogen-agnostic detection) and (2) developing appropriate sample processing and detection algorithms at laboratory scale.

In the past few years, national-scale sampling and data analysis infrastructure has been successfully stood up for pathogen-specific testing purposes. The Traveler-Based Genomic Surveillance program and National Wastewater Surveillance System are examples of such infrastructure.[33]

There is also work being done with pathogen-agnostic detection modalities at laboratory scale: The Centers for Disease Control and Prevention's (CDC's) Advanced Molecular Detection (AMD) office, the Defense Threat Reduction Agency (DTRA), and other parts of the U.S. government have funded work on pathogen-agnostic metagenomics for biodetection.[34] The Nucleic Acid Observatory has also begun developing and testing a sample collection, pre-processing, processing, and data analysis pipeline for metagenomic chimera detection and exponential growth detection on both wastewater and respiratory samples.[35]

The UK government has announced a clinic-based metagenomic early detection system in which National Health Service patients who are suspected of having severe acute respiratory infections will have respiratory samples sequenced rapidly. If this system delivers on its goals, it will be the best example of implementing pathogen-agnostic detection at a large scale.[36] The Global Consortium for Wastewater and Environmental Surveillance for Public Health (GLOWACON), launched by the Health Emergencies Response Authority in the European Union, also has funding for similar work.[37]

Recommendations for Implementing Worked Example Approaches

As in Scenario A, we now present notional high-level recommendations to describe one possible path forward for the U.S. government to increase national resilience to Scenario B: implementing the worked example approaches described previously.

[33] Centers for Disease Control and Prevention, "National Wastewater Surveillance System (NWSS)," last updated November 6, 2024d; Centers for Disease Control and Prevention, "About Traveler-Based Genomic Surveillance," webpage, last updated May 14, 2025a.

[34] Maria Arévalo, Mark Karavis, Adina Doyle, Fran D'Amico, Pierce Roth, Alvin Liem, Samir Deshpande, Jessica Hill, Jackie Harris, Sarah Katoski, and R. Cory Bernhards, "Bioaerosol Surveillance via Untargeted Nanopore Sequencing," poster presented at the U.S. Army Combat Capabilities Development Command Chemical Biological Center, Chemical and Biological Defense Science and Technology Conference, Defense Threat Reduction Agency, 2022.

[35] Nucleic Acid Observatory, "NAO Updates, January 2025," January 9, 2025.

[36] UK Health Security Agency, "UKHSA Launches New Metagenomic Surveillance for Health Security," news release, January 30, 2025.

[37] Health Emergency Preparedness and Response Authority, "Launching GLOWACON: A Global Initiative for Wastewater Surveillance for Public Health," European Commission, March 21, 2024.

The recommendations that follow show *additional* work that might be needed to improve preparedness for Scenario B, on top of meeting all the requirements for Scenario A. Similar to the Scenario A recommendations, these recommendations should be validated with more-detailed work before they are acted on.

Short Term: Preparedness Within One Year

Primary Recommendation

Begin collecting both nasal swab and airplane wastewater samples and processing them with MGS, and develop algorithms to detect novel pathogens from metagenomic data.

If daily nasal swab samples cost $1 each to collect, PromethION flow cells cost ~$1,000 each in bulk,[38] and the cost of staff, sample prep, data processing and storage, and other infrastructure is approximately the same as the total cost of the flow cells (a system with 10,000 daily samples and 172 daily flow cells will cost approximately $354,000 per day, or around $129 million per year).

If wastewater samples cost $10 each to collect, short-read sequencing costs $15,000 for each of 12 required 10B flow cells on the commercial service market,[39] and the cost of staff, sample prep, data processing and storage, and other infrastructure is approximately the same as the total cost of the sequencing runs (a system with daily samples from ten airports will cost approximately $360,000 per day, or around $131 million per year).

These costs are all rough estimates from approximated data and simplified calculations, but we expect that they are within the rough order of magnitude of the actual cost. Both the nasal swab and wastewater detection systems could be expanded further as sequencing costs decrease or to achieve earlier warning.

Testing and Evaluation

We assume that no testing and evaluation are done for short-term preparedness.

Other Recommendation

Explore additional sample sources for this early warning system.

Medium Term and Long Term: Preparedness Within Three to Ten Years

Primary Recommendation

This recommendation is the same as the short-term recommendation.

Testing and Evaluation

We propose four progressive levels of testing.

1. Detection of Simulated Outbreak Reads Added in Silico to Metagenomic Dataset

To assess the performance of the detection algorithm in isolation of any biology or sampling considerations, we suggest adding reads from simulated pathogen outbreaks to a dataset of mNGS reads (ideally, a dataset from real samples rather than a synthetic or computationally generated one). These *spiked-in* reads should initially simulate an engineered pathogen outbreak and, as detection algorithms for non–genetically engineered pathogens are developed, eventually expand to reads simulating a natural pathogen outbreak (made *novel* by temporarily removing the known pathogen from any reference databases consulted by the algorithm.)

[38] Oxford Nanopore Technologies, "Oxford Nanopore Technologies Price List," webpage, undated-d.

[39] Interdisciplinary Center for Biotechnology Research, "NextGen DNA Sequencing: Services," webpage, University of Florida, undated.

If the algorithm can detect simulated outbreaks with a variety of simulated pathogen species and genome lengths, it is likely appropriate to move on to the next layer of testing.

2. Detection of Pathogens Added in Vitro to Respiratory or Wastewater Samples

To assess whether the sample preprocessing and processing steps also perform as desired, we suggest spiking real pathogen surrogates (e.g., genetically engineered bacteriophages and eventually natural bacteriophages) into existing pools of respiratory or wastewater samples. These pathogen surrogates should be spiked in to resemble the relative abundances in each sample that would be expected on the sampling day required to detect the outbreak in time. These sample pools should then be preprocessed and processed according to the early detection system's typical protocol, and the detection algorithm should be run on the resulting dataset of reads.

If the system can detect spiked-in pathogens with a variety of species and genome lengths, it is likely appropriate to move on to the next layer of testing.

3. Detection of Pathogens Added to Wastewater Sources Before Sample Collection

To assess (1) whether the actual relative abundance of pathogens in pooled samples will match expectations and (2) whether enough samples are being collected, we suggest depositing pathogens into the catchment before sample collection at a rate matching the population prevalence requirement. This testing step is likely worthwhile only for wastewater samples because placing pathogens in individuals' noses would likely involve complex safety and regulatory questions. For wastewater samples, this step could entail introducing pathogens into airplane lavatories in the quantities expected while someone is infectious. Samples should then be collected and pooled from across the entire catchment.

If the system can detect deposited pathogens with a variety of species and genome lengths, it is likely appropriate to move on to the next layer of testing.

4. Detection of New Variants of Common Respiratory Pathogens

To assess the performance of the full system once a detection algorithm for non–genetically engineered pathogens is available, we suggest choosing a suite of common respiratory pathogens known to regularly spawn distinct variants (e.g., SARS-CoV-2, influenza A).

If the system can detect new variants of multiple pathogens (ideally with a variety of species and genome lengths) before their estimated population prevalence reaches the threshold from our requirements, we can be reasonably confident that it would be able to detect a Scenario B–like pathogen as expected.

Other Recommendation

Invest in developing novel pathogen detection platform technologies that could detect a wider array of possible threats with lower turnaround time. Early detection systems should be expanded beyond just standard nucleic acid–based pathogens (e.g., prions) to increase resilience against a wider array of possible threats, including ones that are designed to evade detection systems built around standard nucleic acids.

Policy Options

In response to Scenario B, policymakers might consider several opportunities to enhance capacity for detection and supply chain reinforcement. The policy options listed in Table 5.1 that ensure readiness for Scenario A are also applicable to Scenario B. A high-level summary of these recommendations is present in the table. Given the *silent* nature of the Scenario B pathogen, the use of PPE and air decontamination tools to protect VWs, as outlined in the table, is unlikely to be implemented until the pathogen is detected. However,

ensuring there are sufficient quantities produced and stockpiled is also required for protecting VWs in Scenario B.

In addition to the policy options carried over from Scenario A, Scenario B underscores further opportunities for policymakers that are focused on pathogen early warning systems. Existing biosurveillance infrastructure is fragmented and heavily reliant on public-private partnerships, and funding is often tied to public health emergencies. Policymakers might consider sustained funding and investment in strengthening pathogen-agnostic detection systems that can detect asymptomatic infections and novel pathogens while broadening the reach of biosurveillance sampling. As in Scenario A, many of these policy options are not novel; most of these options have been proposed in various forms by others. Future efforts could benefit from the following options:

- **Leverage diagnostic laboratories and clinical settings.** Diagnostic laboratories and clinical settings could be sources of large, sustained funding, providing a potential source for surveillance data. Leftover biological samples (e.g., residue of a sample or medical waste, such as blood serum or respiratory secretions) could be used for pathogen-specific or pathogen-agnostic efforts, such as MGS. As of this writing in 2025, clinical laboratories often reuse (and even resell) leftover samples for quality-control methods prior to disposing of them. However, these could be hugely beneficial to pool for biomonitoring efforts, especially for asymptomatic or presymptomatic infections. Although we have not conducted a thorough review of the regulatory and legal considerations for using leftover samples, this approach may be subject to Institutional Review Board Review and informed consent requirements.[40]
- **Expand existing surveillance programs and partnership efforts.** Existing partnerships that are focused on the detection of novel respiratory pathogen outbreaks, such as the CDC's partnership with Labcorp, could be beneficial.[41] Additionally, investments in next-generation sequencing technologies to strengthen pathogen-agnostic programs, such as those within the Biomedical Advanced Research and Development Authority's Division of Research, Innovation, and Ventures and CDC's AMD program, should be broadened.[42]
- **Leverage CMS to enhance surveillance efforts.** For larger applications within health care settings, a mandate and enforcement structure would be necessary to broaden the scope of medical waste surveillance, requiring a policy change within CMS. Although Medicare does not have direct authority to pay

TABLE 5.1
Summary of Policy Recommendations Carried Over from Scenario A to Scenario B

Policy Recommendation	Details
Increased domestic manufacturing of EHMRs and air decontamination tools	The United States lacks sufficient numbers of EHMRs and air decontamination tools to protect the estimated quantity of VWs. Expanding domestic production through federal-private partnerships and dedicated funding would bolster supply.
Stockpiled EHMRs and air decontamination tools	Once the recommended numbers of EHMRs and air decontamination tools are produced, they should be stockpiled. Stockpiling options include expanding the SNS or creating a separate federal reserve.

[40] Federico R. Lenicov and Nilda E. Fink, "Ethical Issues in the Use of Leftover Samples and Associated Personal Data Obtained from Diagnostic Laboratories," *Clinica chimica acta*, Vol. 548, August 2023.

[41] Centers for Disease Control and Prevention, "2023 Project: Laboratory Corporation of America (Labcorp)," webpage, January 29, 2024a.

[42] Biomedical Advanced Research and Development Authority, "BARDA Announces New Partnerships to Develop Next-Gen Diagnostics for Any Respiratory RNA Virus," webpage, U.S. Department of Health and Human Services, last updated May 3, 2022; Centers for Disease Control and Prevention, "Advanced Molecular Detection (AMD)," webpage, undated.

for public health surveillance, there are two mechanisms to encourage adoption—payment incentives and conditions of participation—that health care organizations must meet to participate in Medicare and Medicaid programs.[43] Either approach would require a newly proposed rule within CMS, published in the *Federal Register* with oversight and approval from the CMS administrator.

- **Implement additional reporting requirements for existing federal programs that engage in surveillance.** Similar to CMS programs that mandate surveillance and reporting of health care–associated infections and laboratory identification, additional reporting requirements could be implemented through the CMS Hospital Inpatient Quality Reporting Program.[44] Such partnerships could be expanded to include additional laboratory networks and health care facilities to broaden biosurveillance efforts in civilian settings, while DoD can opt to strengthen existing surveillance infrastructures.

DoD maintains some of the most robust pathogen early warning programs within the United States and has continued to prioritize such programs through initiatives including the Global Emerging Infections Surveillance (GEIS) program and the Integrated Biosurveillance Branch, which exist in the Armed Forces Health Surveillance Division (AFHSD).[45] The DoD Serum Repository (DoDSR) is an existing program within DoD that could serve as a case study for an established and robust surveillance program, and it can be rapidly expanded for force readiness and resilience.[46] The following components of biosurveillance systems serve as potential opportunities for integration into established force readiness efforts:

- **Sample collection and acquisition and authority for use:** Title 10 of the U.S. Code, Section 1074f,[47] notes the use of pre- and post-deployment blood samples for tracking health concerns, which is done not only for diagnosis, treatment, and prevention but also for health surveillance. Samples are collected during the induction physicals for force protection by DoD authority and are stored in perpetuity with no requirement for informed consent for any future research.[48] DoD Directive 6490.02 reinforces this, noting that "there shall be a Department of Defense Serum Repository for medical surveillance for clinical diagnosis and epidemiologic studies. The repository shall be used for the identification, prevention, and control of diseases associated with military service."[49] The DoD pathogen-agnostic MGS biosurveillance system can be scaled up to include medical waste through several mechanisms—the pre- and post-deployment blood samples as part of DoD Directive 6490.2, which could be expanded to include urine and saliva during medical screenings. Additionally, DoD Directive 6420.02 expanded health surveillance under the Office of the Under Secretary of Defense for Personnel Readiness. Expansion to include medical waste streams from the Military Health Services and TRICARE facilities could

[43] Centers for Medicare and Medicaid Services, "Conditions for Coverage (CfCs) & Conditions of Participation (CoPs)," webpage, last updated September 10, 2024a; Centers for Medicare and Medicaid Services, "What Are the Value-Based Programs?" webpage, last updated September 25, 2024b; Centers for Medicare and Medicaid Services, "Medicare EHR Incentive Program Physician Quality Reporting System and Electronic Prescribing Incentive Program Comparison," fact sheet, last updated May 2013.

[44] Centers for Medicare and Medicaid Services, "Hospital Inpatient Quality Reporting Program," webpage, last updated June 3, 2025.

[45] Military Health System, "Department of Defense Serum Repository," webpage, last updated July 22, 2024.

[46] Military Health System, 2024.

[47] U.S. Code, Title 10, Armed Forces, Section 1074f, Medical Tracking System for Members Deployed Overseas.

[48] Julie A. Pavlin and Robert A. Welch, "Ethics, Human Use, and the Department of Defense Serum Repository," *Military Medicine*, Vol. 180, Supp. 10, October 2015.

[49] Pavlin and Welch, 2015.

also be done by the Assistant Secretary of Defense for Health Affairs via existing mechanisms within DoD Directives 6420.02 and 6490.02E.[50]

- **Sequencing:** GEIS operates a global network of research facilities that perform sequencing; this network could be further strengthened through private-sector partnerships. DoD partnerships with private-sector labs can also be leveraged to increase capacity for additional sequencing.
- **Data analysis and storage:** Scale up GEIS's and DoDSR's existing resources and private-sector partnerships for analysis.
- **Data-sharing and information dissemination:** Use existing GEIS program data-sharing agreements with the AFHSD and Defense Health Agency. External partnerships with the private sector can be used, because DoDSR samples can be released for research purposes outside DoD if the study has a coinvestigator who is assigned to DoD.

Efforts to expand national biosurveillance programs, especially for pathogen-agnostic efforts, are likely to require initiatives across a variety of agencies and collaborators, but these efforts have the potential to significantly increase U.S. capacity to detect novel and emerging biothreats. Deployment of such systems, though, is reliant on sustained funding and the technology to detect known and unknown pathogens. Development and use of pathogen-agnostic metagenomic surveillance systems has been heavily cited as a need for improving post–COVID-19 U.S. bioresilience, but such efforts are dependent on funding for federal programs (e.g., DTRA, the Advanced Research Projects Agency for Health) and public-private partnerships (e.g., the Nucleic Acid Observatory, Ginkgo, LabCorp-CDC).

[50] Department of Defense Directive 6420.02, *DoD Biosurveillance*, Office of the Under Secretary of Defense for Personnel and Readiness, U.S. Department of Defense, incorporating change 1, June 21, 2024; Department of Defense Directive 6490.02E, *Comprehensive Health Surveillance*, Office of the Deputy Secretary of Defense, U.S. Department of Defense, incorporating change 2, August 28, 2017.

CHAPTER 6

Scenario C: Saturating

Chapter Summary

In this chapter, we introduce a scenario with a pathogen that spreads extensively in the outdoor environment. Unlike in Scenarios A and B, this pathogen does not primarily spread from human to human. Instead, airborne particles from outdoor air are the main hazard that VWs (and the general population) must be protected against, posing a different challenge to countermeasures than Scenario A. We propose an initial sketch of possible physical defense approaches that could help prevent exposure to outdoor airborne pathogens, as well as the numerical requirements for those approaches and worked examples of how those requirements could be met: positive pressure filtration–based safe zones and fully encapsulating PPE. We then propose initial recommendations for how the U.S. government could prototype, acquire, and test those defenses.

Overall Shape of Scenario

While Scenario A examined countermeasures that would be challenged by a human-to-human-transmitted infectious disease, this scenario examines countermeasures that would be challenged by **a pathogen that replicates in the environment** and eventually reaches an equilibrium concentration in outdoor air and water and on surfaces.

One possible cause of such a scenario would be *mirror bacteria*: bacteria engineered using macromolecules of the opposite chirality to natural organisms. Because their components would not be recognized by chiral molecules from natural organisms, some mirror bacteria may be able to grow in the environment while evading predators, infect a wide variety of multicellular organisms, and bypass immune responses to continue replicating inside those organisms.[1]

We assume that the pathogen is detected quickly as plants and animals in initially exposed areas begin dying.

Modeling Default Outcomes

Because this pathogen primarily replicates outdoors and infects humans through exposure to contaminated air and surfaces from the outdoors, it is the growth rate of pathogens in the environment that is more relevant than the growth rate of human infections.

Because there are no clearly analogous pathogen scenarios from history, we outline a lower bound on the time it takes to reach this concentration to define a near-worst-case version of this scenario: We assume that

[1] Katarzyna P. Adamala, Deepa Agashe, Damon J. Binder, Yizhi Cai, Vaughn S. Cooper, Ryan K. Duncombe, Kevin M. Esvelt, John I. Glass, Timothy W. Hand, Thomas V. Inglesby, et al., *Technical Report on Mirror Bacteria: Feasibility and Risks*, Stanford Digital Repository, December 2024.

the pathogen will reach this equilibrium concentration **within one year** of initial release. Growth rates of microbes in the environment vary dramatically with differing microbe and environmental characteristics,[2] but we believe this is a reasonable near-worst-case assumption for providing a margin of safety.

Because designing and manufacturing pharmaceutical countermeasures against opposite-chirality pathogens likely will require significant innovation, we assume that pharmaceutical countermeasures are not available according to the timelines of the NBS and are **available only beginning one year after initial pathogen release** if the vital workforce is intact. Therefore, at a minimum, physical defenses for this scenario must protect both VWs *and* the rest of the population for at least one year as outdoor pathogen concentrations rise. **Most VWs will need to go outside and work in existing buildings** where specialized equipment may be located, while the rest of the population shelters in place.

Potential Physical Defense Approaches

The Scenario C pathogen threatens to contaminate environmental sources of all three basic human inputs: air, water, and food. Physical defenses must enable humans to avoid consumption of contaminated inputs for the duration of this scenario.

Avoiding consumption of contaminated water and food is likely simpler than avoiding consumption of contaminated air: any water or food that is stored in sealed containers (e.g., tanks, bottles, cans, or wraps) before the pathogen has begun to spread will remain free of contamination. Water or food potentially exposed to the pathogen can be decontaminated by common methods: boiling or cooking,[3] filtration (for water),[4] or ionizing irradiation (for food at the point of packaging).[5] Because these techniques are already common and efficiently remove environmental microbes from water and food, we do not thoroughly investigate these methods here, although we are not confident that these methods will suffice and we encourage further work to assess in detail how they may fail. We also encourage future work to consider indoor contamination of surfaces by disease vectors, such as pests that infiltrate from outdoors.

Here, we will instead consider the less routine challenge of **avoiding inhalation of contaminated outdoor air**. Two separate forms of physical defenses are necessary to address this challenge: indoor **safe zones** for the entire U.S. population that reduce the equilibrium concentration of indoor microbes relative to outdoor microbes and **PPE** for when VWs must exit safe zones to perform NCFs, such as food delivery. These physical defenses may not be the only ones necessary. We think these two defenses are likely the most unique to Scenario C and worth expanding on in this analysis, but we do not claim that these defenses are sufficient to guarantee protection. We encourage future work to address Scenario C–like situations more thoroughly and consider other challenges and possible solutions that we do not discuss here.

Safe Zones

We define *safe zones* as structures suitable for long-term habitation that would reduce occupants' exposure to airborne pathogens originating from the outdoors. Safe zones can do so with three methods: decontaminat-

[2] Beth Gibson, Daniel J. Wilson, Edward Feil, and Adam Eyre-Walker, "The Distribution of Bacterial Doubling Times in the Wild," *Proceedings of the Royal Society B: Biological Sciences*, Vol. 285, No. 1880, June 13, 2018.

[3] Cleveland County Health Department, "Cooking/Reheating the Food to Kill the Bacteria," fact sheet, undated.

[4] Environmental Protection Agency, *Water Health Series: Filtration Facts*, September 2005.

[5] Centers for Disease Control and Prevention, "How Food Irradiation Works," webpage, last updated February 27, 2024b.

ing outdoor air used for ventilation, reducing the leakage of outdoor air into the space, and decontaminating indoor air.

Decontaminating Outdoor Air Used for Ventilation

To prevent the buildup of carbon dioxide and maintain suitable indoor oxygen concentrations, most buildings require ventilation with outdoor air.[6] (However, there are some exceptions, such as submarines that chemically remove carbon dioxide and add oxygen to the space.)[7]

The outdoor air supply can be decontaminated with mechanical filters or other contained air decontamination techniques, such as GUV.

Reducing Leakage of Outdoor Air into the Space (Unintentional Infiltration)

All buildings have small gaps in the building envelope, and there are two ways to prevent inward leakage of outdoor air through these gaps: sealing and overpressure.

Sealing buildings entails reducing the total area of gaps in the building envelope. The most common *well-sealed* buildings are energy-efficient homes. The main standard for these, Passivhaus, requires buildings to achieve 0.6 or fewer air changes per hour (ACH) of leakage at a 50 Pa (pascal) pressure gradient.[8] With further engineering work, excellent building envelope sealing against larger pressure gradients is possible; NASA's Space Simulation Vacuum Chamber is proof that structures can achieve very low leakage against extreme pressure gradients.[9]

To supplement sealing the envelopes, safe zones can be kept *overpressure*, meaning that the inside of the building is at a higher pressure than the outside. This method can be used to ensure that air always leaks outward rather than inward. This is similar to the technique used by PAPRs and is the inverse of the negative pressure technique used by Biosafety Level 4 (BSL-4) labs to ensure that all air leaks inward rather than outward.[10]

Safe zones can reduce infiltration by reducing leakage area in the building envelope, maintaining overpressure inside the building, or both.

Decontaminating Indoor Air

To complement the two methods mentioned previously, safe zones can also employ the indoor air decontamination strategies described in Chapter 4 to inactivate or remove any outdoor pathogens that do enter the indoor air. (Supplementary surface decontamination can remove pathogens that settle.)

Ingress and Egress

Beyond reducing occupant exposure to outdoor pathogens, safe zones would also need to allow occupants to safely leave and return. These egress and ingress methods could be used to carry sterilized food and water (and other necessary materials) into the safe zone and human waste out of the safe zone.

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[6] Environmental Protection Agency, "How Much Ventilation Do I Need in My Home to Improve Indoor Air Quality?" webpage, last updated May 23, 2025b.

[7] R. Carey, A. Gomezplata, and A. Sarich, "An Overview into Submarine CO2 Scrubber Development," *Ocean Engineering*, Vol. 10, No. 4, 1983.

[8] International Passive House Association, "Passive House Certification Criteria," webpage, undated.

[9] NASA, "World's Largest Vacuum Chamber," February 11, 2009.

[10] Jonathan T. Crane, F. Chip Bullock, and Jonathan Y. Richmond, "Designing the BSL4 Laboratory (Chapter 9)," *Journal of the American Biological Safety Association*, Vol. 4, No. 1, March 1999.

Personal Protective Equipment

As in Scenario A, PPE can also be used to reduce the wearer's exposure to ambient pathogens; such PPE includes both respirators to prevent pathogen inhalation and barrier PPE to prevent pathogen contact with other mucous membranes. However, such PPE does not need to perform a source control function because human-shed pathogens are not the primary hazard source in this scenario.

In addition to protecting workers when they are outside safe zones, PPE can be used to supplement the protection provided inside safe zones. One possible strategy would split safe zones into a component with very high protection levels (to be used for eating, sleeping, and other activities that preclude PPE use) and a larger component with lower protection levels (to be used for work while wearing PPE).

Physical Defense Requirements

Protecting the U.S. population in this scenario requires a combination of safe zones and PPE.

To model the requirements that safe zones and PPE must meet for this scenario, we borrow from Scenario A in using a deterministic model to calculate requirements for reducing the mean VW's exposure to less than one infectious dose over a year, assuming a constant outdoor pathogen concentration. As in Scenario A, we believe that setting requirements using a deterministic model (i.e., the mean of a probabilistic model) is at least as conservative of an approach as setting requirements using the median of a probabilistic model. Reducing the mean VW's exposure to less than one infectious dose should thus ensure that fewer than 50 percent of VWs are infected with the Scenario C pathogen over the course of a year and therefore that the vital workforce remains intact.

Broadly, there are three types of spaces where VWs might spend time:

1. safe zones when VWs are not wearing respirators (e.g., to sleep or eat)
2. safe zones when VWs are wearing respirators (e.g., while working)
3. outdoors when VWs are wearing respirators.

The total number of pathogens that any VW inhales is the sum of the pathogen exposure they incur across the time they spend in each of these three environments:

$$n_t = n_I + n_{I,r} + n_O,$$

where

- n_t = the total number of infectious pathogens inhaled
- n_I = the number of infectious pathogens inhaled during time inside a safe zone when *not* wearing a respirator
- $n_{I,r}$ = the number of infectious pathogens inhaled during time inside a safe zone when wearing a respirator
- n_O = the number of infectious pathogens inhaled during time outdoors when wearing a respirator.

In Boxes 6.1 through 6.4, we expand on each of the terms on the right-hand side of the equation.

Numerical Requirements

To set numerical requirements for a severe Scenario C case, we borrow from Scenario A to set the infectious dose (a single pathogen particle), indoor natural decay rate (approximately zero per hour), and average VW breathing rate (1 cubic meter per hour).

BOX 6.1

Pathogens Inhaled During Time Inside a Safe Zone When Not Wearing a Respirator

The equation for pathogens inhaled inside a safe zone when not wearing a respirator is

$$n_I = c_I b t_I,$$

where

- c_I = indoor pathogen concentration (in pathogens per m^3)
- t_I = time spent inside a safe zone when not wearing a respirator (measured in hours)
- b = breathing rate (measured in m^3 per hour).

To derive the equilibrium indoor pathogen concentration (*CI)* inside a safe zone, we begin with the same differential equation for the instantaneous rate of change of the number of airborne pathogens in a space (n) over a time (t):

$$\frac{dn}{dt} = \textit{rate of pathogens added} - \textit{rate of pathogens removed}.$$

Unlike in Scenario A, there are now two sources of pathogens added to a room: pathogens in the air that is intentionally supplied to a space and pathogens in the air that leaks into a space. Because the volume of air entering the space must equal the volume of air exiting the space, the rate of pathogen removal from ventilation is now coupled with the rate of pathogen introduction.

We therefore expand the differential equation as

$$\frac{dn}{dt} = \left(c_O Q_S(1 - E_S) + c_O Q_L\right) - v\left(n\lambda + \mathrm{nQ_S} + n Q_L\right),$$

where

- c_O is the outdoor pathogen concentration
- E_S is the efficiency of any decontamination method applied to the air supply (from 0 [ineffective] to 1 [perfectly effective])
- Q_S is the volumetric flow rate of the intentional air supply (measured in ACH)
- Q_L is the volumetric flow rate of air leaking into the space (measured in ACH)
- λ is the sum total of airborne pathogen inactivation and the removal rate from natural decay, settling, and indoor air decontamination, but not ventilation
- v is the volume of the space.

When we set $dn/dt = 0$ to solve for the steady state and simplify, this equation becomes

$$\frac{n}{v} = c_I = c_O \frac{Q_S(1 - E_s) + Q_L}{\lambda + Q_S + Q_L}.$$

This equation can be simplified by condensing the combination of decontaminated air supply, leakage, and indoor air decontamination as a single *safe zone protection factor* that is a property of the safe zone (we denote this Z):

$$c_I = \frac{c_O}{Z_I}.$$

BOX 6.2

Pathogens Inhaled During Time Inside a Safe Zone When Wearing a Respirator

The equation for pathogens inhaled inside a safe zone when wearing a respirator is

$$n_{I,r} = \frac{c_{I,r}\, b\, t_{I,r}}{P_{I,r}} = \frac{c_O\, b\, t_{I,r}}{Z_{I,r} P_{I,r}},$$

where

- $c_{I,r}$ = indoor pathogen concentration in spaces where a respirator is worn
- $t_{I,r}$ = time spent inside a safe zone when wearing a respirator
- $P_{I,r}$ = inward protection factor of a respirator worn when inside a safe zone
- $Z_{I,r}$ = the safe zone protection factor of spaces where respirators are worn.

BOX 6.3

Pathogens Inhaled During Time Outdoors When Wearing a Respirator

Similarly, the equation for pathogens inhaled outdoors when wearing a respirator is

$$n_O = \frac{c_O\, b\, t_O}{P_O},$$

where

- t_O = time spent outdoors
- P_O = inward protection factor of a respirator worn when outdoors.

BOX 6.4

Total Exposure

The total number of pathogens (n_t) inhaled by the mean VW must be less than the infectious dose (x) of the pathogen: $n_t \leq x$.

Expanding this inequality to include each of the three pathogen inhalation components,

$$x \geq c_O\, b \left(\frac{t_O}{P_O} + \frac{t_I}{Z_I} + \frac{t_{I,r}}{Z_{I,r} P_{I,r}} \right).$$

We can simplify this equation as the following: $x \geq \frac{c_O\, b t}{R}$, where t is the sum of all time parameters and R can be thought of as the time-weighted average combined protection factor from both safe zones and respiratory protection that must be achieved:

$$R = \frac{t}{\left(\frac{t_O}{P_O} + \frac{t_I}{Z_I} + \frac{t_{I,r}}{Z_{I,r} P_{I,r}} \right)}.$$

We further assume that an extreme upper bound on the final equilibrium concentration of the Scenario C pathogen reaches **a concentration equal to the natural bacterial concentration (bioburden) in existing environmental air**. In other words, its equilibrium concentration in the air in a particular setting will be the same as existing concentrations of airborne bacteria in that setting.

Studies of airborne bacteria concentrations show results that vary widely across locations and times, and these concentrations are especially sensitive to weather events (such as dust and rain storms that cause concentrations to increase by multiple orders of magnitude).[11] Acknowledging this variation, we assume an average outdoor bacteria concentration of 10^6 bacteria per cubic meter, akin to the order of magnitude observed in U.S. populated areas in multiple papers.[12]

Although the *final* outdoor pathogen concentration is thus also 10^6 pathogens per cubic meter, we very roughly assume that the time-weighted *average* outdoor pathogen concentration during the year before the pathogen reaches equilibrium is two orders of magnitude lower: **10^4 pathogens per cubic meter**. (In reality, this figure may be very different, depending on the growth curve of the pathogen.)

The total amount of time a VW spends across all types of space is 1 year (8,760 hours):

$$1 \geq \frac{10^4 * 1 * 8760}{R}.$$

In this scenario, **the average combined protection factor R required is ~10^8**, rounding to the nearest order of magnitude.

Worked Example Approach: Safe Zones and Personal Protective Equipment

In this section, we suggest possible solutions that might meet the required combined protection factor. These are initial worked examples that demonstrate ways that one might work toward a suitable solution, and they should not be considered complete or final solutions. To protect a VW for a year, any combination of safe zone and respirator must satisfy this inequality:

$$10^{-4} \geq \frac{t_O}{P_O} + \frac{t_I}{Z_I} + \frac{t_{I,r}}{Z_{I,r} P_{I,r}}.$$

We explore two possible solutions: a *highly engineered safe zone* meant to reliably protect important personnel, such as those in the U.S. chain of command, and a *widely deployed safe zone* that can protect all other VWs and the general population.

These worked examples take very basic assumptions about the performance of different systems. These examples do not account for failure, user error, or hazards in any media other than the air. We aim to show the types of values needed for each of the subsystems that might be achievable with existing technology,

[11] Viviane R. Després, J. Alex Huffman, Susannah M. Burrows, Corinna Hoose, Aleksandr S. Safatov, Galina Buryak, Janine Fröhlich-Nowoisky, Wolfgang Elbert, Meinrat O. Andreae, Ulrich Pöschl, and Ruprecht Jaenicke, "Primary Biological Aerosol Particles in the Atmosphere: A Review," *Tellus B: Chemical and Physical Meteorology*, Vol. 64, No. 1, 2012.

[12] Robert M. Bowers, Amy P. Sullivan, Elizabeth K. Costello, Jeff L. Collett, Jr., Rob Knight, and Noah Fierer, "Sources of Bacteria in Outdoor Air Across Cities in the Midwestern United States," *Applied and Environmental Microbiology*, Vol. 77, No. 18, September 2011; Aaron J. Prussin II, Ellen B. Garcia, and Linsey C. Marr, "Total Concentrations of Virus and Bacteria in Indoor and Outdoor Air," *Environmental Science and Technology Letters*, Vol. 2, No. 4, March 6, 2015; Tay Ruiz-Gil, Jacquelinne J. Acuña, So Fujiyoshi, Daisuke Tanaka, Jun Noda, Fumito Maruyama, and Milko A. Jorquera, "Airborne Bacterial Communities of Outdoor Environments and Their Associated Influencing Factors," *Environment International*, Vol. 145, December 2020.

not to claim that these designs are optimal or final. Different designs might be optimal under a less severe scenario.

Highly Engineered Safe Zones

A maximally performant safe zone may look like an inverted BSL-4 lab. Whereas a BSL-4 lab is designed to prevent aerosolized pathogens from escaping a building even when those pathogens are aerosolized at high concentrations indoors,[13] this safe zone seeks to prevent high concentrations of outdoor aerosolized pathogens from entering a building.

We imagine that this safe zone is composed of the following three components:

- a well-sealed outer building envelope with indoor recirculating air filtration and a highly filtered air supply (paralleling the highly filtered exhaust air in a BSL-4 lab)
- *inner shelters* protected with additional filtration (paralleling biological safety cabinets inside a BSL-4 lab) that add extra protection and redundance
- an air lock system that allows occupants to leave and return without carrying any outdoor pathogens inside the safe zone (paralleling air locks and chemical showers used in a BSL-4 lab).

Occupants must wear respirators while working inside the outer building envelope, but they can remove respirators once inside the inner shelters (which can be used for eating, sleeping, and other activities that preclude respirators).

One possible design of such a safe zone would retrofit existing warehouses or gymnasiums by

1. **Sealing the building envelope with air barriers, caulk, mastic sealants, and spray sealants.** This might look similar to a thorough Passivhaus envelope sealing. (In this analysis, we consider sealing only as it relates to air currents, although in practice, sealing that is robust to pests, rain, and any other outdoor materials may be necessary.)
2. **Fitting a ventilation system with multistage filtration and supplementary pathogen inactivation, such as GUV.** BSL-4 labs typically use double-stacked high efficiency particulate air (HEPA) filters for exhaust air, which provides better overall filtration and redundancy when compared with a single HEPA filter.[14] HVAC engineers often assume that stacked filters provide linearly additive protection,[15] so the total filtration efficiency provided by n stacked filters, each with efficiency E, can be modeled as $E_{total} = 1 - (1 - E)^n$.
3. **Installing clean bubbles inside the outer building envelope.** These are positive pressure tents that draw air from inside the building envelope and filter it even more. In one embodiment, existing military collective protection (COLPRO) tents could be used for this purpose.
4. **Installing further air decontamination and surface cleaning in the main shelter for additional layers of protection.**

Pathogens Inhaled While Working Inside Outer Building Envelopes

When working inside the outer building envelope but not inside inner shelters, VWs wear respirators. We calculate the expected number of pathogens inhaled for a person working inside the outer building envelopes

[13] Crane, Bullock, and Richmond, 1999.

[14] Crane, Bullock, and Richmond, 1999.

[15] ASHRAE, 2023; Zhonglin Xu, *Fundamentals of Air Cleaning Technology and Its Application in Cleanrooms*, Springer Nature, 2014.

while wearing a respirator for eight hours per day (2,920 hours total) during Scenario C, using the equation in Box 6.2 and parameters in Table 6.1.

An outer shelter with these parameters would have a safe zone protection factor $Z_{I,r}$ of $2x10^{8}$. When a person is in an outer building envelope with these parameters for 2,920 hours, $\frac{t_{I,r}}{Z_{I,r}P_{I,r}}$ becomes $7.3x10^{-8}$.

Pathogens Inhaled While in Inner Shelters

Occupants do not wear PPE when inside inner shelters (Figure 6.1). These inner bubbles use overpressure to significantly reduce the risk of inward leakage and feature additional filtration.

For simplicity, we can assume that the inner shelter has the same design parameters as the outer building envelope, except with only one HEPA filter to decontaminate air supplied from inside the outer building envelope and no respirator. Because the shelters are located inside the outer building envelope, their protection factors are multiplicative with the safe zone protection factor of the outer building envelope (Table 6.2).

An inner shelter with these parameters located inside the outer building envelope described previously would have a combined safe zone protection factor Z_I of $4x10^{12}$. For a person who spends 12 hours per day in these inner shelters (or 4,380 hours total over the course of a year) during Scenario C, perhaps to eat or sleep, $\frac{t_I}{Z_I}$ becomes $1.1x10^{-9}$, using the equation in Box 6.1.

FIGURE 6.1
Highly Engineered Safe Zone Design

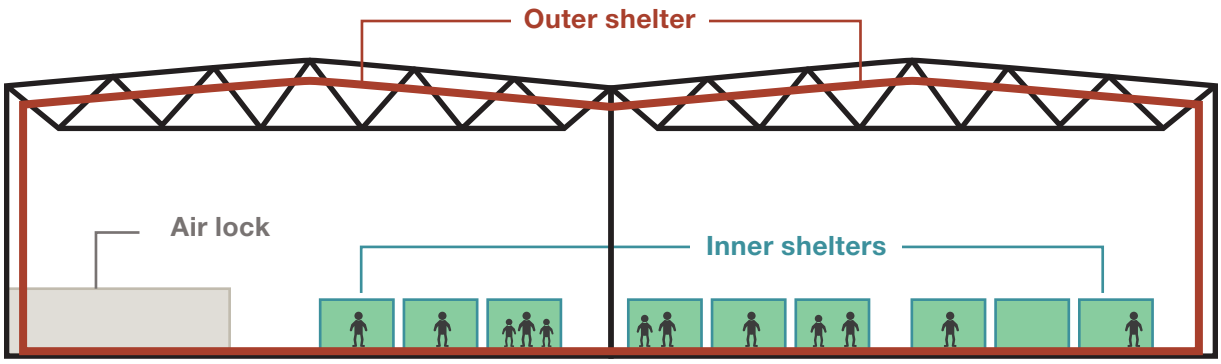


TABLE 6.1
Possible Design Parameters for Outer Building Envelopes

Parameter	Symbol	Chosen design	Value
Outdoor air supply decontamination	E_S	Two stacked HEPA filters (assuming 99.99-percent efficiency for 1-micron particles)	0.99999999
Supply air flow rate	Q_S	Similar to a typical house	1 ACH
Inward leakage	Q_L	Assuming overpressure	0 ACH
Indoor air decontamination	λ	Single recirculating filter	1 eACH
Respirator protection factor	$P_{I,r}$	Elastomeric half-mask respirator	200

TABLE 6.2
Possible Design Parameters for Inner Shelters

Parameter	Symbol	Chosen design	Value
Air supply decontamination	E_S	One HEPA filter	0.9999
Supply air flow rate	Q_S	Similar to a typical house	1 ACH
Inward leakage	Q_L	Assuming overpressure	0 ACH
Indoor air decontamination	λ	Single recirculating filter	1 eACH

Pathogens Inhaled While Outdoors

Outside the safe zone, VWs would be expected to wear PPE. With the remaining 1,460 hours in a year spent outdoors, the protection factor of respirators that VWs must wear becomes over 43.8 million, an extremely high protection factor requirement that no air-purifying respirator is likely to meet. Our existing understanding of the best possible respiratory protection is a fully encapsulating gastight suit worn with a closed-circuit breathing apparatus inside, which should, in theory, have no air exchange between inside and outside the suit (in other words, an infinite protection factor). We do not have an estimate for the performance of these suits in practice, so we encourage further investigation into whether these suits would provide sufficient protection and what other types of PPE could meet this high requirement.

Widely Deployed Safe Zones

Acknowledging budget constraints, it will likely not be possible to produce these highly protective safe zones for the whole population or even all vital workplaces where NCFs must be performed. Instead, the general population can be protected using safe zone kits. While not as reliable as a highly engineered safe zone, these kits would allow sheltering in place and provide occupants with the following:

- airtightening materials, such as sealants and barriers
- ventilation systems designed to fit doorframes with a standardized design for economies of scale
- deployable COLPRO tents (such as the M20A1 room liner)[16] that can be placed in a single room to create a small living space where PPE is not needed to be used for eating, drinking, bodily functions, and sleeping.

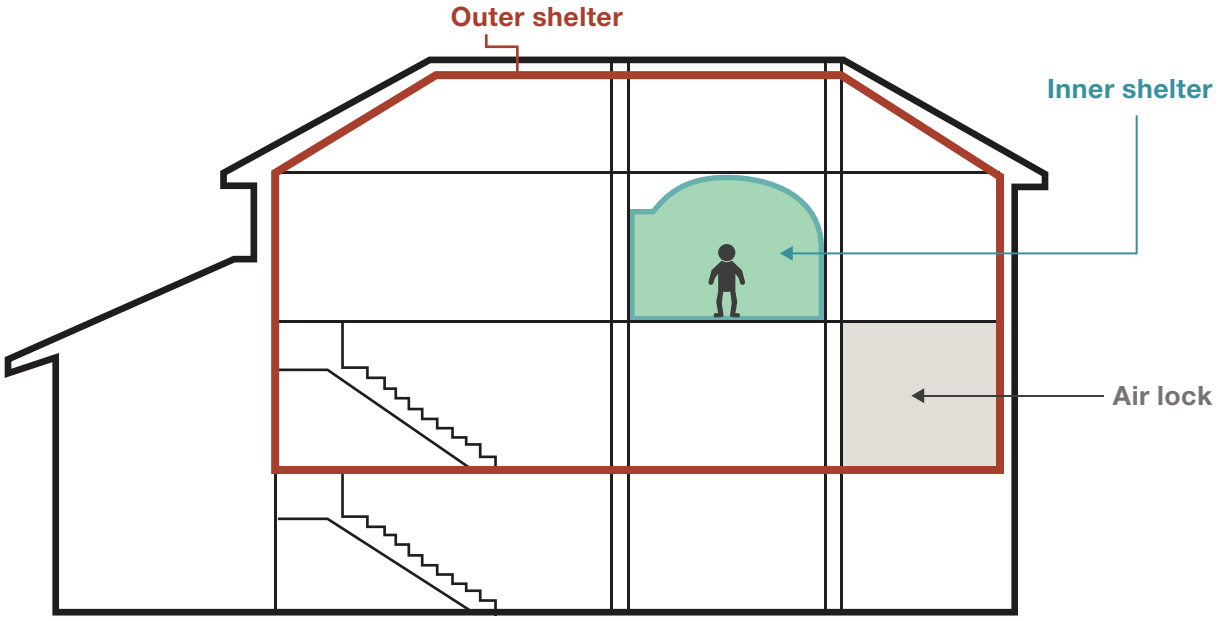
These safe zones can use the same design parameters as the highly engineered safe zones, but VWs can work while wearing PPE inside the outer building envelope (see Figure 6.2).

Ingress and Egress

Between inner shelters and outer building envelopes and between outer building envelopes and the outdoors, there must be effective air locks that remove or inactivate all pathogens in the air. These air locks also must be equipped with surface disinfectants to inactivate or remove any pathogens that may have landed on the PPE worn by entrants or any materials that those individuals are carrying inside.

[16] Michael A. Pompeii, *Joint Service Collective Protection: Commodity Area Overview*, Naval Surface Warfare Center, October 22, 2002.

FIGURE 6.2
Widely Deployable Safe Zone Design Retrofitted to a House



Recommendations for Implementing Worked Example Approaches

Similar to Scenarios A and B, we now describe an initial list of recommendations for one way the U.S. government could attempt to improve national resilience to Scenario C. Because of our additional uncertainties around Scenario C compared with Scenarios A and B, **our main recommendation is a research program** to address key technical questions that could confirm or invalidate the plausibility of using safe zones and PPE to defend against this scenario. We describe some key research questions in Table 6.3.

Following fundamental research, **prototype safe zones should be developed**. These experimental spaces would allow researchers and engineers to test design features and evaluate them for performance.

Once designs have been established and vetted, **high-specification large safe zones should be developed and deployed** for individuals in the critical U.S. chain of command and any VWs needed to immediately preserve that chain of command to ensure that those defenses are available at the beginning of a Scenario C–like event. In addition to building this limited number of highly protective spaces, research should look at effective ways to stockpile or warm-base safe zone precursor materials (e.g., deployable room liners and kits for air-sealing existing structures) so that safe zone capacity can be scaled as soon as a threat emerges. Because it is likely not feasible to stockpile all the materials required to create safe zones at the required scale, effort should focus on making sure that, ahead of a threat, all research and development (R&D) is complete.

Should a threat arrive sooner than the aforementioned steps are completed, emergency deployment and retrofitting of existing spaces could provide some protection. Example emergency steps include sealing warehouses and placing COLPRO tents inside or adapting existing clean rooms to support habitation. In Table 6.3, we present a flow chart summarizing these possible steps.

TABLE 6.3

Recommendations for Future Research on Creating Safe Zones

Analysis Area	Example Research Question or Focus	Description
Base technical analysis: Fundamental pieces of science and engineering research will inform all further research.	Leakage into overpressure buildings	In theory, positive-pressurized spaces should not have inward leakage. Further research needs to evaluate whether this holds true for large spaces and in what ways the assumption breaks down in real cases (e.g., under wind, via the stack effect, or at entry and exit points).
	Efficacy of serial filtration	HVAC guidelines assume that filters placed in series are perfectly multiplicative.[a] However, research completed at Los Alamos National Laboratory in the 1970s suggested that serial filters have diminishing returns.[b] Laboratory experiments should evaluate and more accurately characterize this behavior because it is critical to meeting the high protection-level requirements of the safe zones.
Gap analysis: Our research was limited because specifications and test results for many existing shelters are not public. Researchers with access to this information, especially COLPRO performance results, should complete a full gap analysis.	How much pathogen would leak into a COLPRO tent?	Existing test results and specifications should be evaluated to assess the protection provided by existing COLPRO. If necessary, new testing may be conducted to evaluate performance against a very high-concentration pathogen.
	For how long could a fixed COLPRO be used?	Analysis of fixed COLPRO for protection, long-term habitation, and suitability for upgrade should be completed by DoD.
Siting: We did not cover strategic siting for safe zones. This might consider geographical variation in pathogen concentration, existing infrastructure, or access to logistics networks.	Geographical variation in pathogen concentration	Evaluate where lower pathogen concentrations might be expected. For example, would Arctic regions expect to have lower pathogen concentrations, lowering the protection requirement for safe zones?
	Where is critical infrastructure located, and what buildings can be turned into safe zones?	This analysis should map both the infrastructure that must be protected and which nearby buildings can be quickly retrofitted as safe zones. Mapping logistics networks, energy systems, and other critical infrastructure might also identify central locations that are well placed to protect a high percentage of the VWs at once.
Safe zone R&D: Design, test, and manufacture the key components of the safe zones.	Methods for quickly air-sealing existing structures	Research on barriers, sealants, and associated building techniques should work toward creating a widely deployable kit that can be used to quickly retrofit existing structures to high airtightness levels.
	Developing a widely deployable integrated room liner, air handling, and air lock system	A widely deployable, prefabricated, and integrated room liner, air handling, and air lock system should be developed. This should be designed to be deployed into residential buildings to provide shelter-in-place protection.
Human response: We consider only the engineering feasibility of developing safe zones. Further research must consider the human and social responses to living in safe zones.	Chain of command within and between safe zones	Research should be conducted on how safe zones might communicate with one another and how hierarchy and command will be organized within a safe zone. This is especially important for larger safe zones housing hundreds to thousands of people.
	Psychological response to Scenario C and safe zones	The extreme consequences of Scenario C and the difficulties of living in a safe zone will affect VWs. Understanding the implications of these impacts on these workers and the critical infrastructure that they maintain is essential to a successful response.

[a] ASHRAE, 2023.

[b] Manuel Gonzales, John C. Elder, Marvin I. Tillery, and Harry J. Ettinger, *Performance of Multiple HEPA Filters Against Plutonium Aerosols*, Los Alamos Scientific Laboratory, November 1976.

Testing and Evaluation

Deploying systems that successfully defend against the Scenario C pathogen requires comprehensive testing and evaluation at every stage:

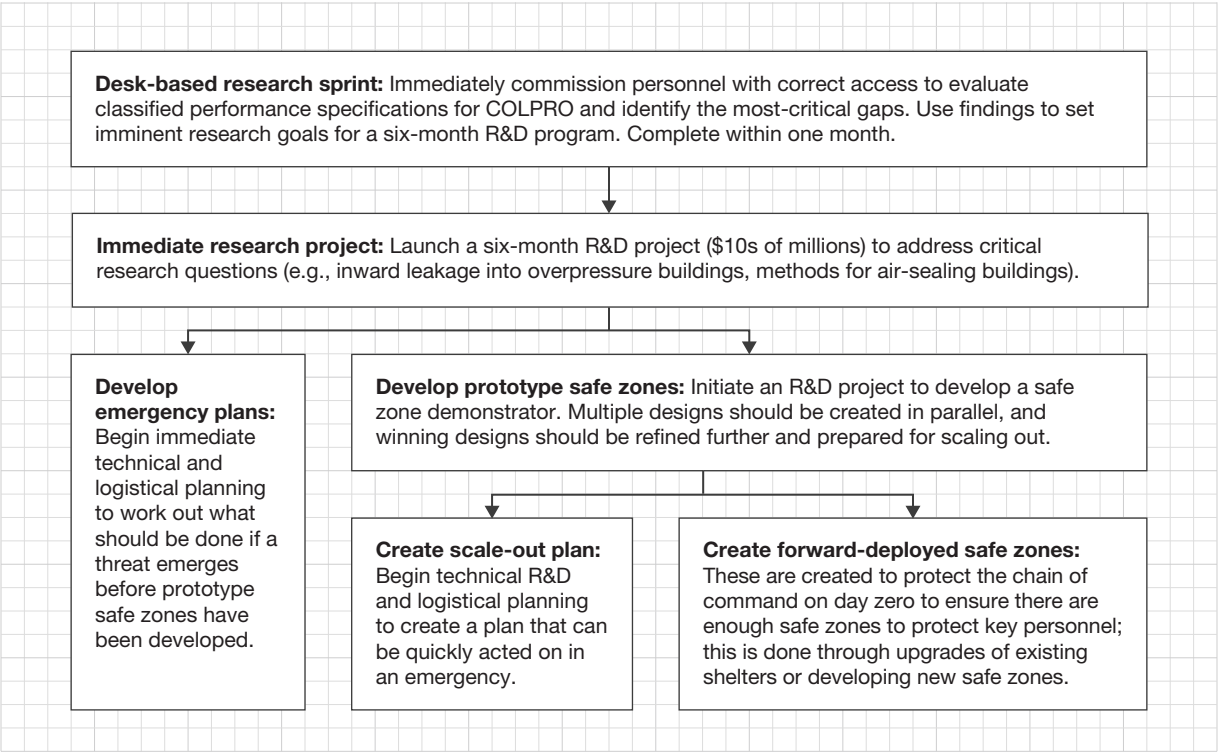
- **System design.** Test various safe zone approaches in advance to establish which of these provide sufficient protection and how they can be improved.
- **Manufacture and assembly.** Conduct quality-control tests during component manufacturing and safe zone assembly to ensure that systems function as intended.
- **Operational.** Implement monitoring systems to detect failures during use, provide early warnings to don PPE, identify failures that require immediate patching, and identify personnel who might need isolation.

Because of the extreme protection requirements for Scenario C, it will likely be difficult to design tests and find instrumentation that can evaluate this performance (see Figure 6.3).

System Design

Further work should evaluate the maximum protection levels that can be evaluated with existing COLPRO testing protocols. If these testing protocols are insufficient to evaluate the protection levels required for Scenario C, they should be expanded or improved. Because of inherent sensitivity limits in instrumentation, whole-system tests may need to be completed with an overconcentrated challenge (i.e., concentrations > 10^7 airborne particles per m^3) or run over extended periods.

FIGURE 6.3
Possible Sequence of Steps to Prepare for a Scenario C–Like Threat



During system design, subsystem tests might be sufficient to establish the likely performance of the whole system. These include but are not limited to tests of air filtration systems against high particle counts and tests of the efficacy of air locks and decontamination protocols with challenge agents.

Manufacturing and Assembly

To reliably maintain high levels of required protection, safe zones and PPE cannot suffer from frequent manufacturing defects. Subsystems must be tested for quality assurance as they are manufactured and assembled, especially considering the scale of production needed for some of these safe zones in the scenario that we describe.

Operational

Systems wear out and components fail. It is inevitable that safe zones will suffer from failures, some unimportant but some critical. To compensate for this, testing must be integrated into the operation of a safe zone. Arrays of sensors can alert occupants to failure of a critical system. Examples might include pressure sensors to detect when the shelter is not at overpressure or particle counters to indicate that the indoor particle count is rising abnormally quickly.

In addition to alarm systems, both automated and manual data can be used to predict failure. Examples might include monitoring pressure changes over the filters to monitor filter saturation.

These monitoring systems might be used to inform immediate actions (e.g., all occupants donning PPE) or be part of a system that informs maintenance. Extensive work must be put into designing systems that can continually monitor the performance of safe zones.

Policy Options

The saturating pathogen described in Scenario C may require safe zone structures to safeguard human populations. These structures should achieve an 8-log protection requirement and be capable of housing and sustaining U.S. civilians for extended periods. At the time of this writing, we are not aware of any structures that have been tested to meet these requirements. To move toward achieving these requirements,

- **Further R&D is needed to test, evaluate, and construct safe zone structures that meet these specifications.** Federal agencies are the appropriate entities to conduct or contract out this type of research. To do so, dedicated appropriations are recommended to ensure that adequate funds are available. Given DoD's expertise in developing military COLPRO units, in-house R&D, and contracting capabilities, this department is an appropriate federal agency to receive and manage the recommended appropriations.

Should adequate safe zone structures be developed to address a Scenario C–like saturating pathogen, these structures—and other necessary supplies and equipment for their operation and to sustain human life—need to be prepositioned for swift and effective deployment. To address this need, the United States could

- **Include safe zones and their component materials in its stockpiles.** Similar to the recommendations for EHMR and portable air-purifying units stockpiling in prior scenarios, the United States could expand the SNS or establish a separate stockpiling mechanism. The benefits and challenges of approaches listed for EHMRs and portable air-purifying units both apply to safe zone stockpiling.
- **Regionally warehouse safe zone structures and other essential supplies.** Stockpiles of safe zone structures should be regionally warehoused. This prepositioning of assets drives down time between their deployment and arrival at target sites. The SNS uses a similar approach and could serve as a model for

safe zones. This structure allows the SNS to begin deploying assets as quickly as 12 hours after a request for assets is granted.[17] These warehouses should also include any supplies required for safe zone operations and other key supplies needed to sustain human life inside these structures.

We also strongly encourage more research and analysis to consider other aspects of Scenario C that we do not consider in detail here, such as contaminated food or water, and the additional physical defenses that might be necessary to counter those hazards beyond safe zones and PPE.

[17] Chemical Hazards Emergency Medical Management, "Strategic National Stockpile (SNS)," webpage, U.S. Department of Health and Human Services, last updated June 18, 2025.

CHAPTER 7

Conclusion

Our goal in this report was to make an initial attempt at describing three severe biological threat scenarios that could challenge the existing defenses in the United States, performing an order-of-magnitude assessment of the technical plausibility of beginning to address them with additional defenses (under a near-ideal societal response), and describing one set of actions that the U.S. government could take to move toward those additional defenses for each scenario.

Our overarching takeaway is that defending against these severe scenarios should *not* be considered impossible. Technologies that could begin to address each scenario are already available, even if further R&D would be beneficial. Although we do not claim that the recommendations or policy options that we propose are the most reliable or cost-effective methods of defending against these threats, we see them as worthy of further investigation and due diligence.

To further validate the recommendations we make, future work should ideally attempt to tighten some of the simplifying assumptions we made at each step of the analysis:

- goal-setting (better estimating the number of VWs)
- scenario-setting (better describing plausible catastrophic pathogens, including additional ones beyond the three we considered here, and detailing their likely effects under existing defenses)
- requirement-setting (better modeling the relevant physical dynamics and accounting for imperfect human and organizational behavior)
- solution-finding (better characterizing potential solutions, their trade-offs, and their likelihood of success).

However, should the United States face severe biological threats before such a comprehensive analysis exists, we hope this work can provide useful guidance on the preparedness actions that the U.S. government could take.

Abbreviations

ACH	air changes per hour
AFHSD	Armed Forces Health Surveillance Division
AMD	Advanced Molecular Detection
APF	assigned protection factor
ASHRAE	American Society of Heating, Refrigerating and Air-Conditioning Engineers
BSL	biosafety level
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
COLPRO	collective protection
COVID-19	coronavirus disease 2019
DNA	deoxyribonucleic acid
DoD	U.S. Department of Defense
DoDSR	U.S. Department of Defense Serum Repository
DTRA	Defense Threat Reduction Agency
eACH	equivalent air changes per hour
EHMR	elastomeric half-mask respirator
FFR	filtering facepiece respirator
GEIS	Global Emerging Infections Surveillance
GUV	germicidal ultraviolet light
HEPA	high efficiency particulate air
HIV	human immunodeficiency virus
HVAC	heating, ventilation, and air conditioning
MCM	medical countermeasure
MGS	metagenomic sequencing
mNGS	metagenomic next-generation sequencing
MPPS	most penetrating particle size
NASA	National Aeronautics and Space Administration
NBS	National Biodefense Strategy
NCF	National Critical Functions
NIAC	National Infrastructure Advisory Council
PAPR	powered air-purifying respirator
PFU	plaque-forming unit
PPE	personal protective equipment
R&D	research and development
RNA	ribonucleic acid
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SNS	Strategic National Stockpile
SWPF	simulated workplace protection factor

UV	ultraviolet
VW	vital worker

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About the Authors

Aman J. Patel is an adjunct research assistant at RAND. He conducts research on biological threat mitigation and resilience. He holds a B.S. in computational neuroscience.

Thomas Milton is the chief executive officer of Amodo Design, a UK-based engineering firm. He is focused on biosecurity, artificial intelligence security, and advancing science. He holds an M.Eng. in bioengineering.

Andrew Graham is the chief technology officer of Amodo Design, a UK-based engineering firm. He is focused on biosecurity, artificial intelligence security, and advancing science. He holds an M.Eng. in mechanical engineering.

Samuel Reynolds is a firmware engineer at Amodo Design, a UK-based engineering firm. He is focused on biosecurity, artificial intelligence security, and advancing science. He holds an M.Sci. in physics.

Ulrik Horn is an independent researcher and founder of Fønix, a company developing infrastructure resilient to mirror bacteria outbreaks. His technical research focuses on atmospheric and aerosol science and technology, particularly aerosol dispersal and removal, as well as near-boundary wind behavior. He holds a B.A. in mechanical engineering and applied mechanics.

John P. Tarangelo is a senior technical analyst at RAND. His research focuses on health security, biodefense, and biosecurity policy. He holds an M.S. in public health microbiology and emerging infectious diseases.

Saskia Popescu is a policy researcher at RAND focused on global health security and pandemic prevention risks. Her research addresses converging biosecurity risks, including artificial intelligence bio and antimicrobial resistance conflict security, as well as critical infrastructure resilience to high-consequence diseases and enhancing biosurveillance. She holds a Ph.D. in biodefense.

Greg McKelvey, Jr., is a senior physician policy researcher at RAND. His research focuses on implications of artificial intelligence for national security. He holds an M.D. and M.P.H.