2

Estimated Future Mortality from Pathogens of Epidemic and Pandemic Potential

Nita K. Madhav, Ben Oppenheim, Nicole Stephenson, Rinette Badker, Dean T. Jamison, Cathine Lam, and Amanda Meadows

ABSTRACT

Epidemics and pandemics pose a sporadic and sometimes severe threat to human health. How should policy makers prioritize preventing and preparing for such events, relative to other needs? To answer that question, this chapter uses computational epidemiology and extreme events modeling simulations to estimate the risk of future mortality from low-frequency, high-severity epidemics and pandemics in two important categories: respiratory diseases (particularly those caused by pandemic influenza viruses and novel coronaviruses) and viral hemorrhagic fevers such as Ebola and Marburg virus diseases. The simulations estimate global annual averages of 2.5 million deaths attributed to respiratory pandemics and 26,000 viral hemorrhagic fever deaths, 72 percent of which are estimated to occur in Africa. Annual averages conceal vast year-by-year variation, and the reported analyses convey that variation, as well as variation across regions and by age. The estimates suggest higher frequency and severity of such events than previously believed and that this chapter likely provides a lower-bound estimate given the chapter's focus on deaths caused by a subset of pathogens. The simulations suggest that an event with the mortality level of COVID-19 (coronavirus) should not be considered a "once in a century" risk, but rather as having an annual probability of 2–3 percent (that is, occurring on average once in 33–50 years). Despite the substantial uncertainty in heavy-tail distributions, policy makers can use these estimates to develop risk-informed financing, prevention, preparedness, and response plans.

INTRODUCTION

Long before the emergence of COVID-19 (coronavirus), policy analysts described pandemics as a "neglected dimension" of global security because of the persistent underfinancing of fundamental aspects of prevention and preparedness (Jamison et al. 2013; Sands, Mundaca-Shah, and Dzau 2016). Several high-level panels convened in the midst of the COVID-19 pandemic called for large increases in global spending on health system strengthening, surveillance, and preparedness (Sirleaf and Clark 2021). Although vital, these recommendations contend with an entrenched pattern of panic and neglect marked by a strong tendency for sporadic health emergencies to spark short-term attention and investment, which tails off all too rapidly once the crisis has passed.

The slide from panic to neglect happens in part because policy makers operate under uncertainty; they lack estimates of the probability of epidemics—including pandemics—that would enable them to prioritize preparedness for such events relative to other needs (refer to table 2.1 for definitions of epidemic, pandemic, and other terms used in this chapter). Consequently, epidemics and pandemics tend to be treated as random and unpredictable phenomena rather than events for which decision-makers can perform rigorous analysis, estimate costs, and prioritize investments.

Table 2.1 Key Terms and Abbreviations

Term	Definition used in this chapter
Average annual loss	The expected loss (in this chapter, deaths) per year. Refer to annex 2A for further details on its calculation.
COVID-19	A coronavirus disease caused by SARS-CoV-2, beginning in 2019.
Direct mortality (or direct deaths)	Deaths caused by primary infection with a pathogen and any immediate secondary effects resulting directly from that infection. This chapter measures direct mortality from the time when an epidemic begins to when transmission ceases.
Epidemic	"The occurrence in a community or region of cases of an illness . . . clearly in excess of normal expectancy" (Porta 2014, 93).
Event catalog	A collection of historical or modeled events and associated data on event parameters and outcome estimates (Madhav, Stephenson, and Oppenheim 2021).
Exceedance probability function, annual	A function, also known as an "EP curve," providing the probability that an event of a given severity or worse will begin within a given year. For the purposes of this chapter, severity is measured in terms of deaths.
Excess mortality (or excess deaths)	"The mortality above what would be expected based on the non-crisis mortality rate in the population of interest."[a]
Normalized deaths	Deaths per 10,000 population. Also referred to in this chapter as population normalized deaths.
Pandemic	"An epidemic occurring over a very wide area, crossing international boundaries, and usually affecting a large number of people" (Porta 2014, 209). References in this chapter to epidemics include pandemics as well. That is, all pandemics are epidemics, but not all epidemics reach the level of becoming pandemics.
Respiratory diseases	Diseases that affect the lungs and other parts of the respiratory system.[b] Respiratory diseases of pandemic potential constitute one of the two disease categories modeled in this chapter. The modeled pathogens include pandemic influenza and novel/epidemic coronaviruses.

table continues next page

Table 2.1 Key Terms and Abbreviations (continued)

Term	Definition used in this chapter
Return period	Inverse of annual exceedance probability—that is, the average time between events of a given magnitude or greater (also known as return time or recurrence interval). (Refer also to box 2.2.)
Risk	The quantitative combination of the following information: (1) what can occur, (2) the probability that it can occur, and (3) the potential magnitude of consequences that can result (Kaplan and Garrick 1981).
Spread risk	Risk that a pathogen spreads from person to person.
Tail risk	Risk of low-probability, high-impact events (Cirillo and Taleb 2020). (Refer also to box 2.1.)
Viral hemorrhagic fevers (VHFs)	Diseases caused by viruses that damage organ systems, leading to hemorrhaging.[c] VHF epidemics constitute one of the two disease categories of events modeled in this chapter. The modeled pathogens include Ebola, Marburg, and Nipah viruses.
Zoonotic pathogen	"An infectious pathogen or parasite that originates in (or is maintained in the wild by) one or more non-human hosts, but can be transmitted to and cause disease in humans" (Han, Kramer, and Drake 2016, 567). The process by which a zoonotic pathogen is transmitted to a human being is called "zoonotic spillover."
Zoonotic spillover (or "spark") risk	Risk of transmission of an animal pathogen to a human. (Refer also to the definition of "zoonotic pathogen" in this table.)

Source: Original table created for this publication.

a. World Health Organization, "Global excess deaths associated with COVID-19 (modelled estimates)," https://www.who.int/data/sets/global-excess-deaths-associated-with-covid-19-modelled-estimates.

b. National Cancer Institute, *NCI Dictionary of Cancer Terms*, "Respiratory disease," https://www.cancer.gov/publications/dictionaries/cancer-terms/def/respiratory-disease.

c. US Centers for Disease Control, "About Viral Hemorrhagic Fevers," https://www.cdc.gov/viral-hemorrhagic-fevers/about/?CDC_AAref_Val=https://www.cdc.gov/vhf/about.html.

Moreover, because the benefits of preparing for infrequent events are often invisible, policy makers often choose to prioritize preparedness for high-probability events rather than for rare ones (Lempert and Light 2009). To grapple with the threat posed by infrequent, severe epidemics, analysts should adopt a risk-based approach to decision-making, more akin to methods used for other natural catastrophes. Emergency planners and policy makers are already accustomed to thinking about natural catastrophes, such as floods and earthquakes, in terms of their frequency and severity (FEMA 2016); however, this discipline has not generally translated into public health planning.

A key objective of this chapter is to reduce some dimensions of uncertainty in the analysis of epidemics and pandemics by applying principles of risk management. To do so, it presents a framework through which probabilities can be estimated sufficiently to guide decision-making.

Although not typically used to plan for epidemics, this framework could be used to change the dominant paradigm for risk assessment and preparedness planning.

Adopting the most cost-effective strategies to prevent, prepare for, and respond to epidemics requires an understanding of their anticipated frequency and severity—that is, the level of risk that they pose. Interventions such as strengthening disease surveillance systems, investing in lab and diagnostic capacity, and developing new vaccine platforms, production systems, and supply chains might have a modest benefit-cost ratio if severe pandemics are merely a "once in a century" risk. If the

risk is substantially greater, however, such interventions might be very cost-effective strategies to protect global health and reduce mortality. The risk estimates in this chapter allow decision-makers to approximate the necessary level of epidemic preparedness measures, and to identify which measures would be most cost-effective, both during and between epidemic periods.

This chapter presents estimates of the mortality risk of potential future epidemics caused by key respiratory pathogens and viral hemorrhagic fevers (VHFs). It offers new estimates and analyses of simulations, underscoring the substantial risk posed by epidemics. In the third edition of *Disease Control Priorities* (*DCP3*), Madhav et al. (2017) presented risk estimates focusing on pandemic influenza—only one, albeit critical, pathogenic risk with pandemic potential. This chapter expands on that foundation and updates the risk estimates provided in *DCP3* to include estimates for a broader set of epidemic risks. It incorporates new data and scientific advances into model enhancements, developed in part to support multilateral agencies, governments, philanthropic organizations, and the private sector. These enhancements also account for underreporting in epidemiological data and adjust for demographic changes since Madhav et. al (2017) was originally published.

Although many pathogens are capable of sparking large infectious disease events (for example, pandemic influenza viruses, Zika virus, coronaviruses, HIV, cholera, dengue virus, and more [Madhav et al. 2017]), the focus of the analysis in this chapter is based in part on the framework of Fraser et al. (2004) for assessing the controllability of epidemics caused by different pathogenic threats. In that framework, risk of an uncontrollable epidemic increases with human-to-human transmission efficiency and decreases with detection probability. This chapter therefore focuses on a subset of pathogens that meet these criteria and account for the majority of risk: respiratory diseases, notably those caused by pandemic influenza viruses and epidemic or novel coronaviruses. It also presents estimates for VHFs, encompassing filoviruses (such as Ebola and Marburg viruses) and Nipah virus. These pathogens are of global concern and meet some aspects of the criteria in Fraser et al. (2004) because of their potential for causing asymptomatic infection (Diallo et al. 2019) and evading detection (Glennon et al. 2019).

Several other categories of infectious disease threats, although recognized as important, were considered to be outside the scope of this chapter and were thus not included in the analysis:

- *Endemic diseases*, even if they can enter epidemic phases (for example, seasonal influenza, HIV/AIDS, and malaria), because these diseases have well-understood, frequently occurring patterns of losses
- *Vector-borne diseases* (for example, Zika and dengue), because their geographic ranges are constrained by climatic and ecological factors
- *Bacterial diseases*, including those arising from antimicrobial resistance, because treatment methods exist (although this chapter's estimates of direct deaths for viral respiratory diseases include bacterial co-infections)

- *Other nonviral diseases* (for example, prions and fungi), because they have limited geographies, modes of transmission, and transmission efficiency
- "*Unknown unknowns*," or diseases caused by pathogens not thought to have the potential to infect humans, or those wholly unknown to science. It is important to bear fully in mind the significance of unknown unknowns: not so very long ago, HIV/AIDS would have fallen into this category.

The chapter also does not model risk from bioterror (deliberate release of infectious agents) or bio-error (accidental release of infectious agents, for example from laboratory accidents), because doing so would require additional modeling efforts incorporating, for example, the characteristics, capabilities, and strategies of terrorist organizations, and biosafety protocols and practices within specific laboratories. These factors can be explicitly modeled and linked with the broader risk modeling framework presented here but are beyond the scope of the present analysis (refer to chapter 4 in this volume for a discussion of biosafety and biosecurity).

Although epidemics can lead to many adverse outcomes—including infections, hospitalizations, deaths, societal disruption, educational delays, and economic shocks—this chapter focuses on deaths. It includes neither morbidity estimates nor estimates of the impacts of long-term sequelae, although they are important topics. The considerable welfare losses caused by epidemics and pandemics—including economic damages (refer to Fan, Jamison, and Summers 2017) as well as losses to education and to livelihoods, and trauma and psychological damages—require distinct modeling techniques and are beyond the scope of this chapter. This chapter focuses on deaths because they are the most readily measurable, observable, and reported metric, and therefore provide a less biased indicator of epidemic severity than other metrics such as infections or hospitalizations.

Given all of these considerations, the estimates presented in this chapter are not intended to capture the totality of epidemic risk. Rather, they should be interpreted as a lower-bound estimate of the potential loss from such events.

Drivers of Epidemic Risk

Risk modeling is not simply an exercise in mathematics; it must appropriately represent real-world processes, and modelers should have familiarity with the complex web of underlying factors shaping the risk. The modeling framework for this chapter therefore explicitly incorporates several critical drivers of epidemic risk, including zoonotic spillover, global travel patterns, and governance challenges. The following paragraphs provide background information about these processes; annex 2A provides specific details of how they are incorporated into the models for this chapter.

Nearly all modern pandemics have sparked when zoonotic pathogens have jumped from animals to humans, often through activities such as hunting, habitat encroachment, and intensive livestock farming (Jones et al. 2013; Olival et al. 2017).

Multiple studies show that epidemics, especially those caused by zoonotic spillover events, are increasing in both frequency and severity (Jones et al. 2008; Smith et al. 2014). For a subset of high priority viruses, this trend is exponential, meaning not only that epidemics are becoming more frequent and more severe but also that spillover-driven epidemics are occurring at an accelerating rate (Meadows et al. 2023). Climate change and other forms of anthropogenic environmental change, such as deforestation and habitat fragmentation, are predicted to increase the frequency of zoonotic spillover events because they increase the frequency of contact between humans and animal reservoir species (Carlson et al. 2022).

Increasing human population density and connectivity through global travel and trade facilitate the spread of the outbreaks (Baker et al. 2021). The accessibility of global air travel makes effective containment of emerging outbreaks increasingly difficult because infected individuals can disperse over large geographic distances before cases are detected and reported to public health officials (Meslé et al. 2022). For example, rapid geographical spread was well-documented in the severe acute respiratory syndrome (SARS, caused by SARS-CoV-1) outbreak of 2003. In a hotel in Hong Kong SAR, China, 1 individual infected 10 others, 6 of whom took international flights to Australia, Canada, the Philippines, Singapore, and Viet Nam. These traveling secondary cases subsequently led to SARS outbreaks in Hanoi, Singapore, and Toronto within a few days of the first reported case in Hong Kong SAR, China (Cherry 2004). Similarly, during the COVID-19 pandemic, early detection of SARS-CoV-2 variants occurred in airline passengers (Wegrzyn et al. 2022). Spread by air travel also occurred during the 2014 West Africa Ebola epidemic (Gomes et al. 2014).

Evidence from serial infectious disease epidemics occurring in fragile and conflict-affected areas, perhaps most notably the 2018 North Kivu Ebola virus disease epidemic in the Democratic Republic of Congo, provides a clear reminder that conflict and instability can facilitate infectious disease transmission. Armed conflict can degrade disease surveillance systems, creating blind spots and lengthening the period during which disease transmission can occur before it is detected and mitigation measures are put in place (Wise and Barry 2017). Insecurity and violence can also increase the risk of disease transmission by facilitating population displacement (Price-Smith 2001) and by impeding public health response activities through operational disruptions, destruction of public health facilities and equipment, and direct attacks on public health personnel (Jombart et al. 2020). Public distrust of government institutions can also reduce compliance with disease control measures such as immunization campaigns and contact tracing, potentially leading to increased morbidity and mortality (Bargain and Aminjonov 2020; Farzanegan and Hofmann 2022; Vinck et al. 2019).

Techniques for Estimating Risk

Apart from research published in *DCP3*, scant scientific literature exists dedicated to estimating the frequency and severity of infrequent, high-consequence epidemics

(Fan, Jamison, and Summers 2017; Madhav et al. 2017). In contrast to the well-described methods for estimating risk and burden of endemic and frequently occurring diseases, major public health or infectious disease epidemiology textbooks do not explore the quantification of risk—especially tail risk (refer to box 2.1)—from more sporadically-occurring epidemics (Bennett, Dolin, and Blaser 2019; Nelson and Williams 2014). Contributions on this topic have instead come from interdisciplinary research teams or the private sector (Cirillo and Taleb 2020; Marani et al. 2021; Wilkinson 2021). The relatively limited public health literature on the prospective analysis of risk and burden posed by epidemics is perhaps attributable to the multidisciplinary nature of the problem, and the development of estimation techniques within fields that have had limited interaction with public health researchers.

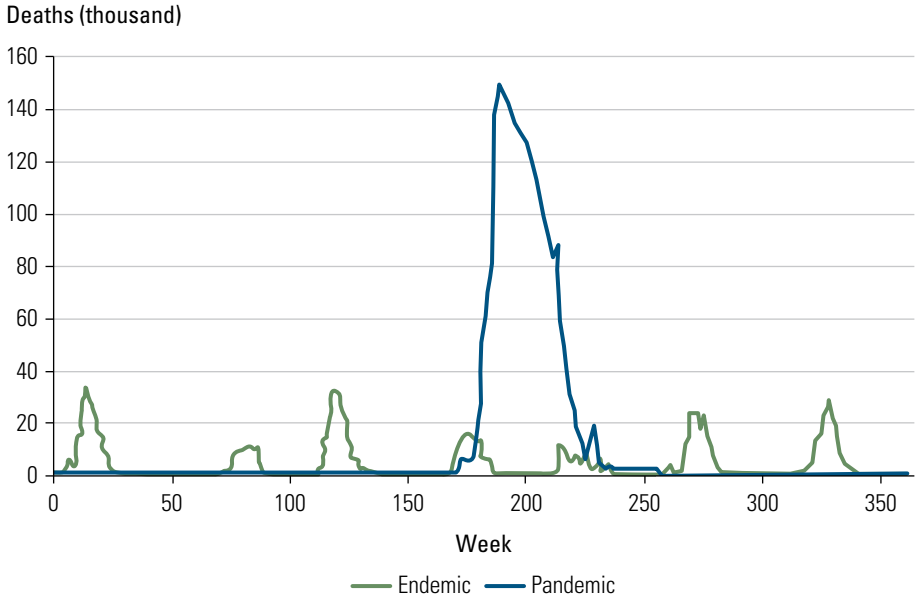
Following the conventions from *DCP3*, this chapter provides risk estimates in the form of exceedance probability functions (EPFs) (Madhav et al. 2017). An EPF can be analyzed to estimate the probability that an event of a given severity or worse will start in a given year, and other metrics of interest, such as the average annual loss (AAL). Modelers can estimate EPFs using empirical data from historical events, or use simulated data from modeled events. Empirical EPFs derived from historical data are most appropriate for pathogens that cause frequent outbreaks or that have a recurrent or seasonal pattern (for example, seasonal influenza or meningococcal meningitis). A historically derived empirical EPF may be misleading when historical data are sparse, marked by underreporting, or include unincorporated trends that could influence future expected losses (Madhav, Stephenson, and Oppenheim 2021). For those reasons, the EPFs for this chapter were generated using a probabilistic modeling approach that generates an event catalog containing simulated events.

Historical Data Analysis

Historical data are often the first point of reference for evaluating future risk. Although historical data can offer valuable insights, constructing a view of future risk based on empirical data can be misleading, especially for infrequent events. This section highlights the factors that can make historical data an unreliable indicator of future risk, demonstrating the rationale for taking an extreme events modeling approach to quantify the risk.

Figure 2.1 shows a hypothetical time series of historical data. In the graph, it is possible to see the differences between endemic disease patterns as compared to pandemic disease patterns. In this hypothetical 360 weeks—roughly seven years—of data, the endemic disease occurs regularly throughout the time period in a relatively well-characterized pattern. By contrast, a pandemic event occurs in a single spike spanning approximately one year. Interestingly, in this graph, both the endemic disease and the pandemic disease actually have similar AALs, but have very different characteristics of frequency and severity that lead to those annual average values.

Figure 2.1 Example Comparison of Timing and Magnitude of Endemic versus Pandemic Deaths



Source: Original figure created for this publication.

For frequently occurring infectious diseases with well-characterized historical patterns, historical data can yield acceptable estimates of future risk. For instance, the historical record on pandemic influenza, despite having important limitations, does provide evidence of several major events per century (Morens et al. 2010). Historical data analysis can reveal changes over time, such as increasing frequency and severity of events, rate of increase, and factors that drive this dynamic (Meadows et al. 2023). Techniques for estimating risk solely on the basis of historical data include, for example, statistical and actuarial modeling and parametric curve fitting (Embrechts, Resnick, and Samorodnitsky 1999).

The historical record, however, represents only a small subset of the possible events that can occur, especially for low-probability, high-severity events. It therefore represents a limited sample size, which can lead to erroneous conclusions about what could occur in the future (box 2.1). The absence of empirical data in the form of observed events can be mitigated somewhat by considering counterfactual events (Resolve to Save Lives 2021), but such events do not necessarily provide information about how severe an event would have been had it occurred. Pandemics are relatively rare, and they show large variations in severity. For example, consider the vast difference in mortality between the 1918 and 2009 influenza pandemics.

Box 2.1

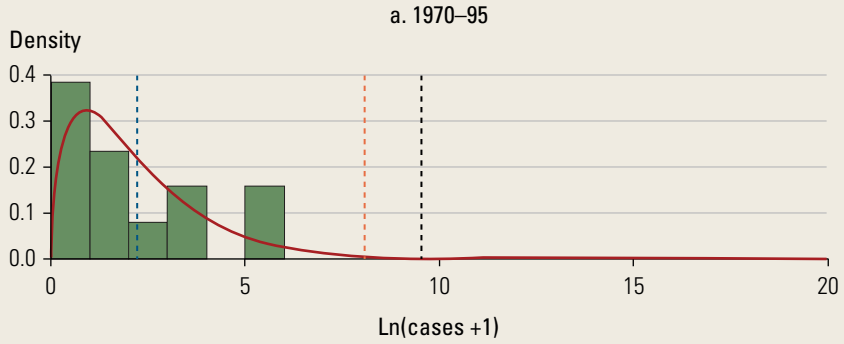
The Importance of Tail Risk

The severity distribution of epidemics is highly skewed, exhibiting a very long "tail," consisting of very rare, severe events. When a highly skewed distribution provides only a small sample of data points (in this case, historical events), the "heaviness" of the tail is often underestimated. This underestimation is problematic because appropriately planning for future events requires an accurate understanding of expected losses—especially those caused by less frequent, highly damaging events.

Figure B2.1.1 shows the distributions of cases from historical high-consequence, zoonotic spillover events (Meadows et al. 2023), and how the fitted distribution changes over time with the addition of more events. As more events occur over time, the tail of the distribution (defined as the upper 1 percent) gets longer and heavier, which shifts the expected value (mean) of the distribution as well as the range and expected value of the tail, to the right. There are two explanations for this finding: (1) as the sample size increases over time, the sample distribution and mean get closer to the true distribution, or (2) the true distribution becomes more skewed over time, meaning that events get more severe. The true cause is likely a combination of these two factors. This shift could be further influenced by changes in diagnostic capacity, which may increase detection of less severe outbreaks and would push the mean of the distribution toward a lower value, but could also increase the number of identified cases in larger outbreaks, pushing the mean higher.

The estimation of tail risk affects decision-makers' preparedness planning. When decision-makers have limited resources and need to directly weigh epidemic impact against other health risks, properly accounted-for tail risk is critical to understanding the expected value of future losses. In addition, carefully quantifying tail risk can help decision-makers assess and properly plan for low-frequency, high-severity events. Using epidemiological data and computational modeling makes it possible to supplement historical data with simulated events. These simulations can then provide additional data points on which to base the loss distribution, and allow for a more robust estimation of the tail.

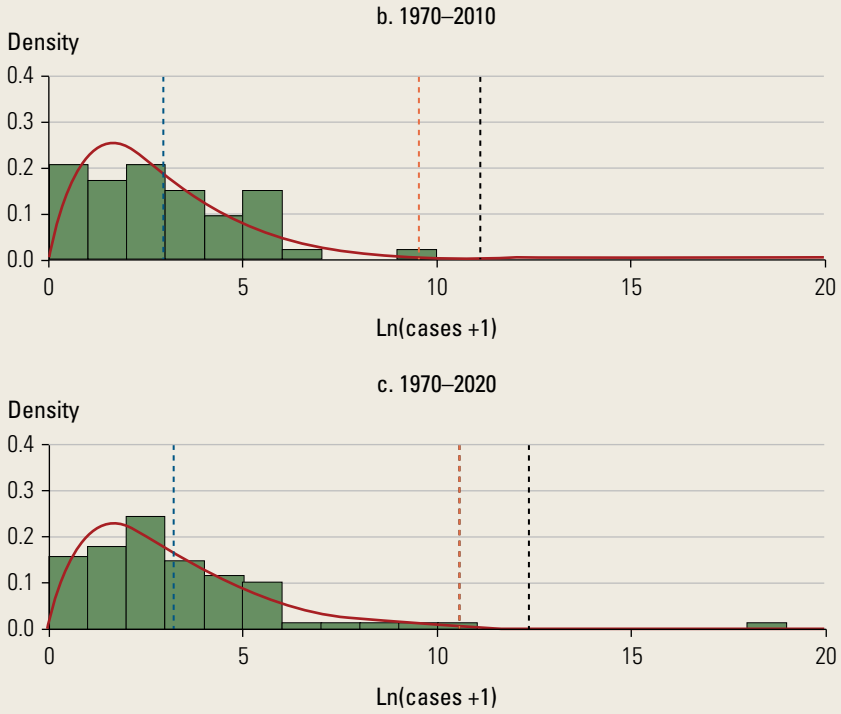
Figure B2.1.1 Distributions of Historical High-Consequence, Zoonotic Spillover Cases per Outbreak over Time, 1970–2020



box and figure continue next page

Box 2.1 The Importance of Tail Risk (continued)

Figure B2.1.1 Distributions of Historical High-Consequence, Zoonotic Spillover Cases per Outbreak over Time, 1970–2020 (continued)



Source: Original figure created for this publication.

Note: The x-axis shows a natural log transformation of the number of cases +1. The "tail" is defined as the upper 1 percent of the probability density function. The red line shows the fitted probability density function, the blue line shows the expected value, the orange line shows the 99th quantile, and the black line shows the expected value of the tail. Ln = natural log.

The many challenges and biases found in reported epidemiological statistics further complicate the construction of a historical view of epidemic risk (Badker et al. 2021). These factors can lead to data inconsistencies and lack of comparability across different information sources, which further compounds the uncertainty in these estimates. These challenges occur for all types of epidemic data, including for respiratory and VHF events.

In addition to data challenges, the underreporting of many diseases leads to biased estimates of severity and is particularly problematic in resource-limited settings (Glennon et al. 2019). Underreporting is driven by many factors including disease symptomology and severity; contextual conditions (such as local clinical capacity), which can influence mortality rates; public health and disease surveillance infrastructure; sociocultural factors (such as stigma attaching to particular symptoms or diseases); and government censorship (Meadows et al. 2022).

Extreme Events Modeling

Extreme events (or "catastrophe") modeling can overcome the challenges of using historical data to develop risk estimates for infrequent, high-severity events, known as "tail risk" (Cirillo and Taleb 2020). For example, the (re)insurance industry routinely consults with modeling experts in natural hazard fields such as meteorology, seismology, hydrology, and volcanology for this purpose (Kozlowski and Mathewson 1995). However, these extreme event modeling techniques tend to be taught within, and used by, intellectual communities that have limited cross-pollination with public health actors.

Extreme event modeling techniques build on historical data as a starting point and use extensive mechanistic modeling and simulation to fill in the gaps beyond the available historical data. The extreme events modeling framework also enables analysts to assess the influence of inputs that may not exist in the historical record but are biologically and epidemiologically plausible. For example, even if a vaccine or treatment option has not yet been widely used but could potentially be deployed in reaction to an outbreak, simulation models can include this intervention when appropriate.

When extreme event modeling techniques are applicable, effective use of this modeling approach still involves substantial technical and analytical requirements. Extreme event models typically require significant computational infrastructure and resources, have many parameters to estimate, and for epidemics, unlike for natural hazards, must account for the effects of human behavior in shaping the course of events.

METHODS USED IN THIS CHAPTER

This section provides details about the multidisciplinary modeling approach used to generate risk estimates and associated metrics including AALs and EPFs. It also discusses important considerations for modeling total deaths rather than excess deaths or reported deaths, and provides information on potential limitations and uncertainty in the modeled estimates.

Risk Estimation Process

The risk modeling approach used to develop the estimates in this chapter draws from principles in computational epidemiology, social science, extreme events modeling, actuarial science, and other fields to produce millions of simulated epidemics and pandemics. The process requires developing probability distributions for each model parameter, statistically sampling values from these parameter distributions, seeding each simulation with these parameter values as initial conditions, and then simulating the spatio-temporal spread of the events through a global, stochastic, metapopulation disease spread model that incorporates information about population vulnerability, mobility patterns, medical technology, preparedness levels, and intervention measures. Annex 2A provides comprehensive details of the methods used for this chapter.

In these simulations, an event is considered to be active until transmission ceases, whether through stochastic die-off, herd immunity, public health and social measures (formerly called nonpharmaceutical interventions), or other phenomena. The simulations include only the acute portion of the events and do not include any transition to an endemic state. This assumption reflects the lack of consistent epidemiological standards to select cutoff points indicating the transition from epidemic to endemic state. Consequently, the loss estimates represent a lower bound; they do not capture ongoing mortality from endemic transitions, in which a pathogen enters a seasonal or cyclic pattern with an ongoing and persistent mortality burden, as occurred during the 1918 influenza (Taubenberger and Morens 2006) and COVID-19 pandemics (Contreras, Iftekhar, and Priesemann 2023).

The simulation process results in model event catalogs, each containing 100,000 simulated years and encompassing millions of infectious disease scenarios, which are used to estimate the risk from epidemics. Note that the event catalogs for this chapter do not project 100,000 years into the future but, rather, represent 100,000 versions of "next year." These catalogs are generated separately for both respiratory diseases and VHFs, and the results are also divided in this way. This division is maintained for ease of interpretation, because deaths from respiratory diseases account for the vast majority of expected deaths from the epidemics modeled. There are orders of magnitude of difference between the levels of potential losses caused by these disease categories, and combining them would obscure this asymmetry. Additionally, different types of response measures may be more relevant and cost-effective for combatting each disease category—for example, mass vaccination efforts and medical oxygen for respiratory diseases versus ring vaccination and safe burials for VHFs—and are easier to tease apart when loss estimates are separated.

These event catalogs are used to produce several estimates, including AAL (measured in deaths), population normalized deaths, exceedance probabilities (EPs), and age- and region-specific mortality estimates (region definitions are shown in map 2.1 and annex 2B). The AAL estimates—that is, the expected value of annual losses—are shown as normalized deaths per 10,000 population and deaths in thousands. Population numbers come from the United Nations' World Population Prospects 2022 release, using a reference year of 2020, for a total estimated global population of 7.8 billion (UN DESA 2022).

In addition to annual estimates, cumulative exceedance probabilities (CEPs) are also estimated over periods of y years using the formula

$$CEP = 1 - (1 - EP)^{y} \qquad \text{(Equation 2.1)}$$

where y is the time horizon of interest. In this chapter, the time periods of interest are 5, 10, and 25 years; however, the CEP can be computed over any potential time period (for example, over the lifetime of a person born next year and expected to live to the current global life expectancy of approximately 73 years). The CEP is thus another, potentially more useful, way of conveying the same information as the annual EP estimates. It demonstrates the potentially large cumulative risk posed by rare events and estimates risk for time durations of greater interest to policy makers.

The CEP estimates for this chapter contain significant assumptions but likely represent a reasonable lower bound for medium-term pandemic risk. The CEP formula assumes that the risk remains constant at current levels and that each year of the time period is independent. The CEP estimates therefore assume that there are no changes to underlying drivers of risk that could affect the frequency and severity of future epidemics. Current trends, however, suggest that infectious disease risk is increasing (Meadows et al. 2023), driven by increasing human-wildlife contact, deforestation, urbanization, intensifying demand for animal protein, and intensifying international travel (Baker et al. 2021; Carlson et al. 2022). The estimates here likewise do not incorporate assumptions about the potential beneficial impact of new vaccine platforms, improvements to global infectious disease surveillance, early warning, and preparedness. On balance, though, the risk is probably higher over the medium-term future than the assumption of constant risk implies. Annex 2C contains a sensitivity analysis that shows how differing assumptions of future risk would change the estimated CEP.

Direct Deaths versus Excess Mortality

The modeled deaths presented in this chapter are total direct deaths, rather than reported deaths or excess deaths. For the purposes of this chapter, direct epidemic deaths are considered to be those caused directly by primary infection with the pathogen and any immediate secondary effects resulting directly from that infection (for example, pneumonia resulting from infection with pandemic influenza).

It is important to be explicit about what counts as a direct death in this chapter. The chapter adopts nomenclature from the assessment of the World Health Organization (WHO) of the number of deaths associated with COVID-19 (Msemburi et al. 2023). WHO begins with the concept of "excess deaths," which it defines as the difference between an estimate of actual deaths in the period under consideration and an estimate of what the number of deaths would have been had past trends continued. WHO's COVID-19 excess mortality estimates were calculated by taking the difference between observed all-cause mortality and expected mortality in 2020–21. Expected mortality was modeled by projecting monthly all-cause mortality data from 2015–19 to 2021. Msemburi and colleagues estimate global excess deaths in the COVID-19 years of 2020 and 2021 to have been 14.8 million—2.7 times the 5.42 million reported global deaths from COVID-19 during that same time period (table 2.2). They partition these excess deaths into four categories, A–D:

A. Strictly non-COVID-19 deaths (for example, from other external events such as wars or natural disasters)
B. Indirect COVID-19 deaths (for example, deaths occurring from health system overload)
C. Direct COVID-19 deaths that were not reported
D. Direct COVID-19 deaths that were reported (5.42 million).

Table 2.2 Excess Death and Reported COVID-19 Death Totals, by Region, January 2020–December 2021

Region	Excess deaths per 10,000 population (WHO modeled)	Reported deaths per 10,000 population	Excess-to-reported death multiplier
Global	19	7.0	2.7
India	34	3.4	10
Sub-Saharan Africa	11	1.3	8.5
Central Asia	14	2	7
Western Pacific and Southeast Asia	12	3.4	3.5
Middle East and North Africa	19	6.6	2.9
Central and Eastern Europe	59	24	2.6
Latin America and the Caribbean	35	24	1.5
North Atlantic	18	17	1.1
United States	28	25	1.1
China[a]	–0.37	0.04	–9.2

Source: Original calculations based on Msemburi et al. 2023 (excess deaths per 10,000 population) and WHO 2022 (reported deaths per 10,000 population).

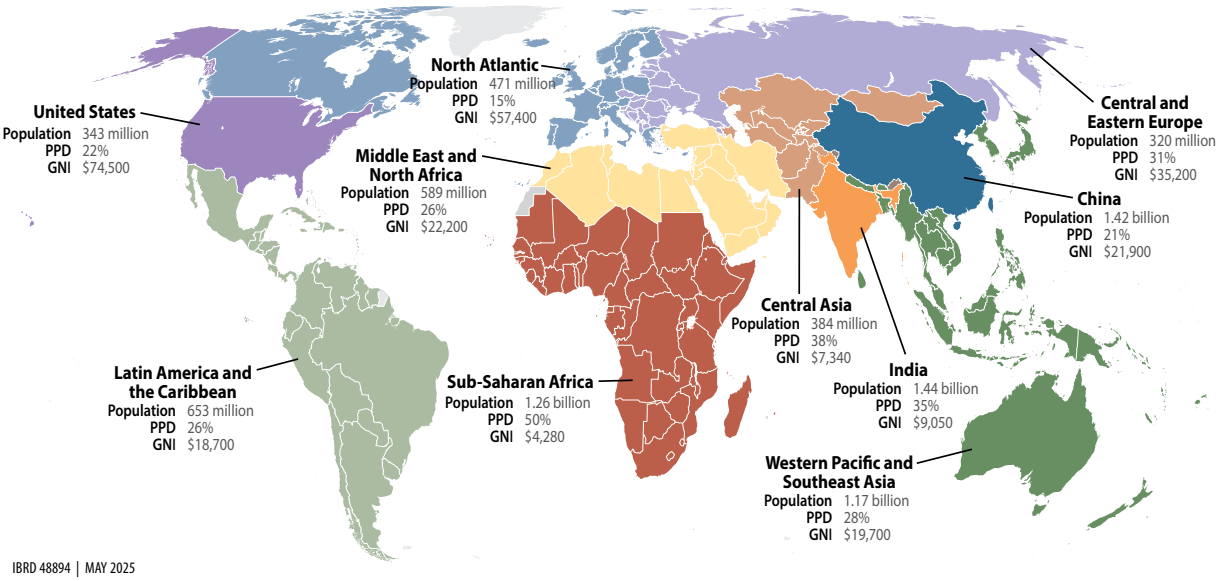
Note: Numbers in the table are rounded to two significant digits. For details on regional groupings, refer to map 2.1 and annex 2B. WHO = World Health Organization.

a. Excess mortality in China greatly increased in December 2022 (after the time frame of the analysis) following decisions to end a national policy that incorporated extensive testing and public health and social measures to reduce transmission, and excess deaths for the entirety of the pandemic would be substantially higher than these estimates.

The excess mortality estimates also account for any deaths that were averted thanks to pandemic-related changes in social conditions and personal behaviors (for example, fewer traffic deaths because of reduction in travel and working from home, or fewer influenza deaths because of COVID-19 mitigation strategies such as masking and stay-at-home orders). In some countries (such as Australia, China, Japan, and New Zealand), it was estimated that a higher number of deaths were averted because of pandemic-related behavioral changes than were directly or indirectly attributable to COVID-19, resulting in a net negative excess mortality during the 2020–21 study time period. However, substantial changes in disease control policies and disease transmission from 2022 onward led to substantial increases in mortality; incorporating data from this time period could substantially alter the understanding of the regional distribution of excess mortality from COVID-19.

The WHO analysis attempts no estimate of the division of the 9.4 million excess deaths not reported as COVID-19 deaths (14.8 million – 5.4 million) among the categories (A), (B) and (C). Msemburi et al. (2023, 136) do observe that "the greater proportion of excess deaths can be attributed to COVID-19 directly." The risk modeling results provided in this chapter include both reported and unreported direct deaths; that is, they represent the sum of categories (C) and (D). Although WHO does not report that sum directly, a number consistent with Msemburi et al. (2023) would be 11 million to 12 million direct COVID-19 deaths in 2020–21.

Map 2.1 Regional Grouping of Countries



Source: Image based on Jamison et al. 2024.

Note: Annex 2B lists the countries in each region. GNI = gross national income per person, 2021 international dollars; PPD = probability of premature death, dying before age 70 (2023); PPP = purchasing power parity.

Limitations and Uncertainty in Model Estimates

Models are abstractions of the real world. Therefore, the approach taken for this chapter has, by necessity, some limitations. First, historic data are limited; and, despite the great care taken to mitigate this challenge with the modeling approach, it is not possible to fully account for gaps and biases in historical data. Second, there are many parameters to estimate, all of which have substantial uncertainty. Third, the outcomes of pandemics are affected by human behavior and movement patterns, which can vary substantially in specific socioeconomic contexts and subpopulations, or could change over time in surprising ways that may not be fully accounted for or characterized in the model. Fourth, models do not fully account for secular trends such as the apparent increase in zoonotic spillover events that can spark pandemics, or amplification patterns that could arise from the intersection of trends in spillover with the intensification of climate change.

It is worth emphasizing that, despite extensive model diagnostics and validation—including sensitivity analyses, benchmarking of historical events, and cross-referencing against other data sources—substantial uncertainty attaches to the estimates in this chapter. This uncertainty results in part from the historically informed probability distributions from which key parameters for the simulations are drawn. Additionally, substantial uncertainties exist in the underlying structure of the models and factors used here, which might influence the future evolution of parameters in ways poorly reflected in history.

In this chapter, 95 percent confidence intervals (CIs) for deaths are estimated by sampling one thousand subsets of 10,000 years each from the broader 100,000-year model event catalogs and estimating the 2.5th and 97.5th percentiles from the samples. As such, the CIs convey the uncertainty in catalog sampling, rather than the full universe of uncertainty. Because of the relatively small width of the estimated CIs for the AAL estimates, and the larger uncertainties that surround the analysis, the chapter does not report CIs for the AAL, because it has the potential for conveying false precision.

CIs associated with the EP estimates are also calculated; these CIs typically fall in the range of 5–20 percent of estimated values, and expand to 40 percent or more of estimated values as one goes further into the tail of the EPF. An important feature of the EPF is that the CIs widen markedly as one moves further out in the tail of the curve. This widening is expected; estimates for extremely rare, massive pandemics are inherently uncertain, given their sparsity.

Further uncertainty is found in the extreme tail of the EPF because of the model's assumptions regarding socio-behavioral responses during epidemics. These assumptions might not hold true under extreme, high-severity scenarios. For example, in a truly massive event, there could potentially be very intense governmental and societal responses to curtail transmission. Major social change could occur (for example, mass quarantine or compulsory licenses of vaccine intellectual property), leading to better outcomes than estimated here. Conversely, the possibility exists that, during a truly massive pandemic, there could be a total societal collapse, which would lead to vastly worse outcomes than estimated here.

Because of the deep underlying uncertainties, the estimates in this chapter—particularly estimates of risk decades into the future—should not be interpreted as conveying great precision. Rather, the headline numbers reflect broad ranges consistent with historical evidence and state-of-the-art modeling.

RESULTS: RESPIRATORY DISEASES

The following subsections provide estimates of global mortality from future epidemics and pandemics caused by the modeled respiratory diseases. These estimates are presented in terms of AALs, EPFs, and the distribution of loss estimates, demonstrating the skewed nature of the distribution. The subsections also present regional mortality estimates and mortality distributions by age groups.

Global Respiratory Mortality

The estimated AAL from future epidemics and pandemics caused by the modeled respiratory diseases is approximately 2.5 million deaths. The AAL provides a summary measure of the scale of potential losses. Rather than representing the number of deaths that occur each year, the AAL arises from a pattern of events that exhibit larger amounts of deaths that occur more sporadically and in a punctuated

manner, including years having 0 or very low levels of loss (figure 2.1). Within the respiratory event catalog, pandemic influenza viruses are the predominant contributors to the losses, contributing nearly twice as much to the AAL as epidemic/novel coronaviruses (table 2.3).

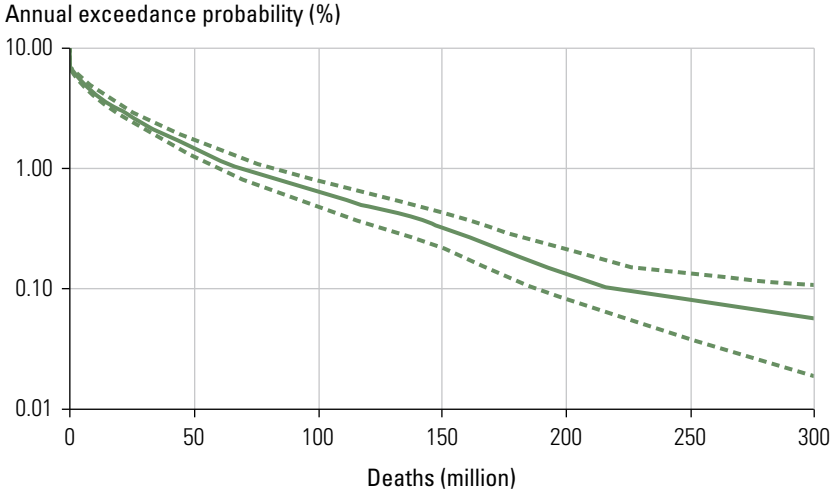
An inspection of the EPF shows a heavily skewed (that is, asymmetrically overdispersed) distribution of loss estimates (figure 2.2 and table 2.4). Smaller events are more likely to occur, but larger events—even larger than those historically observed—are also possible and represented further out in the tail of the distribution. As the probability decreases (or return period increases—refer to box 2.2), the number of deaths shows an initial, rapid increase, but then decelerates as one moves further into the tail of the distribution. The steep rise in event severity is apparent in the higher-frequency (that is, lower return period) portion of the curve, perhaps most visibly in the large jump in the number of deaths between the 10- and 20-year return periods. Although the steepness of the rise decreases further out in the tail, the tail events contribute substantially to the skewness of the distribution (box 2.2). The steep rise and heavy tail of the curve are consistent with the potential for wide transmission and global spread of respiratory diseases.

Table 2.3 Global Average Annual Deaths Based on Respiratory Event Catalog

	Average annual deaths	
	Count (thousand)	**Per 10,000 population**
Pandemic influenza	1,600	2.0
Epidemic/novel coronaviruses	890	1.1
Total	2,500	3.2

Source: Ginkgo Biosecurity simulations.

Figure 2.2 Global Respiratory Exceedance Probability Function Based on Respiratory Event Catalog



Source: Original figure created for this publication.

Note: The solid line depicts the point estimates, and the dashed lines depict the 95 percent confidence interval.

Table 2.4 Selected Exceedance Probabilities and Associated Global Deaths Based on Respiratory Event Catalog

Return period (years)	Exceedance probability	Deaths per 10,000 population (95% CI)	Death counts (thousand) (95% CI)
5	0.20000	0.001 (0.001, 0.001)	0.53 (0.50, 0.55)
10	0.10000	0.002 (0.002, 0.002)	1.4 (1.2, 1.5)
20	0.05000	7.2 (5.4, 10)	5,600 (4,300, 7,700)
35	0.02857	28 (23, 32)	22,000 (18,000, 25,000)
50	0.02000	45 (39, 53)	35,000 (30,000, 42,000)
100	0.01000	86 (74, 100)	68,000 (58,000, 80,000)
200	0.00500	150 (120, 180)	110,000 (100,000, 140,000)
333	0.00300	200 (160, 220)	150,000 (130,000, 170,000)
500	0.00200	220 (200, 260)	170,000 (150,000, 200,000)
667	0.00150	250 (210, 290)	190,000 (170,000, 220,000)
1,000	0.00100	280 (240, 390)	220,000 (190,000, 300,000)

Source: Ginkgo Biosecurity simulations.

Note: CI = confidence interval.

Box 2.2

Rolling the Dice

Mathematically, the return period is the inverse of the exceedance probability (the probability that an event of a given severity or worse will begin within a given year). For example, a 1 percent annual exceedance probability—that is, a 1 percent chance of observing an event of a given severity (or worse) in a year—translates to a 100-year return period or, alternatively, a "1-in-100 year event" (FEMA 2016). Although the return period is a convenient way to conceptualize the estimates presented in this chapter, it can also be misinterpreted in ways that encourage decision-makers to underinvest in preparing for low-probability, high-severity events, by assuming (implicitly or explicitly) that the risk is "tomorrow's problem."

It is all too easy for even informed analysts to misinterpret frequency estimates for rare events. A 100-year return period does *not* mean that the level of loss occurs once per 100 years, nor does it mean that the losses are evenly spaced out at 100 year intervals. A "1-in-100 year event" simply means that the event statistically has a 1 percent chance of starting in any given year. That is, a given event is expected to occur, on average, once in repeated samples of 100 year time periods. It is even possible to have multiple "100-year" events occur during a 100-year period. With this explanation in mind, any given year is a roll of the dice.

The EPF is also used to estimate the level of mortality found at different EPs (table 2.5). Box 2.3 presents an in-depth look at the likelihood of an event having mortality of a comparable magnitude to the COVID-19 pandemic.

Table 2.5 Exceedance Probabilities for Selected Global Death Levels Based on Respiratory Event Catalog

Global severity		Likelihood	
Death counts	Deaths per 10,000 population	Return period (years)	Exceedance probability (%)
> 800	> 0.001	7	14
> 80,000	> 0.01	15	6.8
> 8,000,000	> 10	22	4.5
> 80,000,000	> 100	120	0.8

Source: Ginkgo Biosecurity simulations.

Box 2.3

COVID-19: Not a "Once in a Century" Pandemic

The panic and neglect cycle is driven, at least in part, by the historic fact that severe pandemics occur infrequently. Although the twenty-first century has seen multiple pandemics, including the 2009 pandemic influenza and Zika virus, the last public health crisis seemingly comparable in impact to COVID-19 was the Great Influenza of 1918 (Johnson and Mueller 2002). Because COVID-19 occurred nearly 100 years after the 1918 pandemic, some commentators have described pandemics of this scale as occurring "once in a lifetime" (Guterres 2020) or even "once in a century" (Cruickshank and Shaban 2020; Gates 2020; WHO 2020) .

At the end of December 2022, the end of the third year of the pandemic, there were over 660 million reported cases and 6.5 million reported deaths globally from COVID-19.[a] Based on our simulated event catalog, the annual probability of an event of this mortality level or larger is estimated to be 2–3 percent. In other words, every year there is a 2–3 percent chance that an event equal to or more severe than COVID-19 (in terms of mortality) could occur. Expressed in terms of return periods, it would be a 33- to 50-year event, rather than a 100-year event (box 2.2). Assuming that the level of risk does not change, the chance (cumulative exceedance probability) that an event having a mortality level as severe as or worse than COVID-19 will occur over the next 5 years is estimated at 10–14 percent, over the next decade at 18–26 percent, and over the next 25 years at 40–53 percent.

COVID-19 was more severe than other recent respiratory pandemics, such as the 1957, 1968, and 2009 influenza pandemics. However, comparing COVID-19 to the 1918 influenza pandemic, which many have done, sets up a false equivalency. As a percent of global population mortality, the 1918 pandemic was orders of magnitude more severe than COVID-19. It led to the deaths of up to 5 percent of the global population as compared to the estimated 0.08 percent global mortality from COVID-19 as of December 2022, based on reported deaths (refer to table 2A.13 in annex 2A).

The estimates in this chapter of the frequency and severity of pandemics, rooted in extreme events modeling techniques, demonstrate that COVID-19 is not likely to be a "once in a century" pandemic. On the contrary, over the next 25 years, a pandemic with a mortality level similar to or worse than COVID-19 has a roughly 50 percent probability of occurrence, similar to flipping a coin.

a. Ginkgo Biosecurity, "Spatiotemporal Data for 2019-Novel Coronavirus Covid-19 Cases and deaths," Humanitarian Data Exchange, https://data.humdata.org/dataset/2019-novel-coronavirus-cases.

Because severe respiratory pandemics occur sporadically and have a relatively low (perceived) probability of occurrence in any given year, policy makers tend to underinvest in preparedness (Sands, Mundaca-Shah, and Dzau 2016). Viewed over a longer time horizon—but one still relevant to policy makers and planners—the substantial magnitude of the risk from rare, potentially catastrophic events becomes more apparent (table 2.6). For example, the annual probability of a respiratory pandemic killing at least 10 million people worldwide is estimated at 4.2 percent; however, over a 10-year period, the probability of such an event occurring is 35 percent. Extrapolated further, the results suggest that, over the next 25 years, there is a 66 percent probability of a respiratory pandemic that would kill 10 million people or more, with the caveat that many of the assumptions in the risk modeling approach have greater uncertainty over a longer time period (refer to table 2C.1 in annex 2C).

Although the respiratory model event catalog contains a wide range of event sizes, the vast majority of the risk from respiratory disease pandemics is estimated to fall in the tail of the EPF: low-probability, high-impact events. Approximately 50 percent of the simulated events in the catalog are very small, with an average magnitude of 120 global deaths. Roughly 4 percent of events have 8 million or more global deaths. Only 0.6 percent of events have global death tolls exceeding 100 million. Strikingly, however, the comparatively small number of high-magnitude events heavily drive the estimates of expected mortality. The 1.4 percent of catalog events with death totals exceeding 50 million account for 68 percent of all deaths in the respiratory catalog (figure 2.3 and table 2.7). And, although the higher-frequency events (return periods of 35 years or less) make the lowest contribution to AAL as measured in deaths, they can still cause substantial economic disruption (Madhav et al. 2017).

Respiratory Mortality by Region

Respiratory diseases have a substantial expected impact on all geographies, but risk is unevenly distributed (refer to map 2.1 and annex 2B for information on the regional country groupings). To reduce the effects of different population age structures by region, in addition to the counts and normalized AALs, the age-standardized AALs per 10,000 population were also calculated, using the WHO 2000–25 Standard Population (Ahmad et al. 2001). The highest age-standardized AAL occurs in Sub-Saharan Africa and the lowest in the North Atlantic region (figure 2.4 and table 2.8).

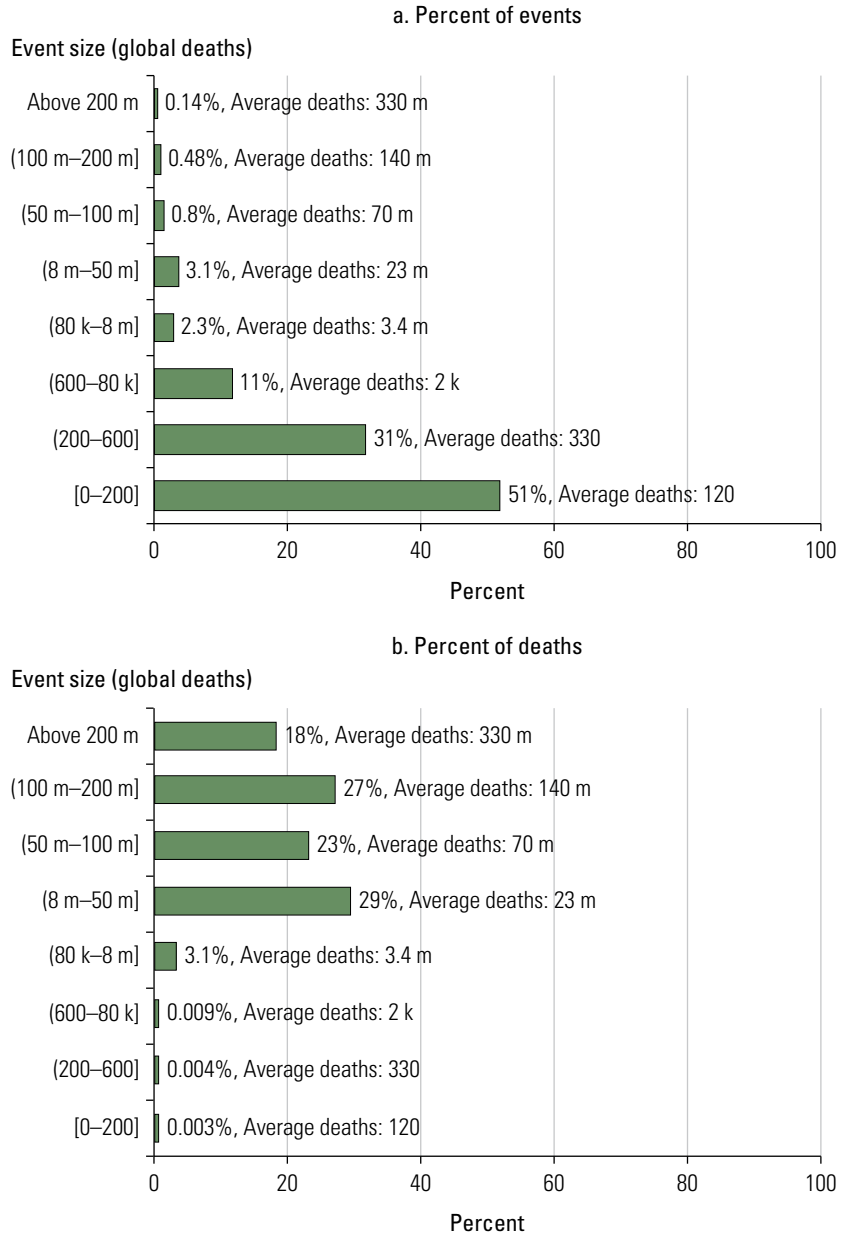
Table 2.6 Annual, 5-Year, 10-Year, and 25-Year EP Estimates for Selected Global Event Sizes Based on Respiratory Event Catalog

Deaths	Annual EP (%)	5-year EP (%)	10-year EP (%)	25-year EP (%)
1,000,000	6.3	28	48	80
10,000,000	4.2	19	35	66
25,000,000	2.6	12	23	48
100,000,000	0.6	3.0	5.8	14

Source: Ginkgo Biosecurity simulations.

Note: EP = exceedance probability.

Figure 2.3 Respiratory Event Catalog Composition: Simulated Event Sizes and Their Contribution to Expected Losses



Source: Original figure created for this publication.

Note: The parentheses and brackets notation follows the international standard ISO 80000-2:2019(en) Quantities and units—Part 2, which conveys the following meaning. The "(" indicates the range is exclusive of the number, while "[" and "]" indicate the range is inclusive; k = thousand; m = million.

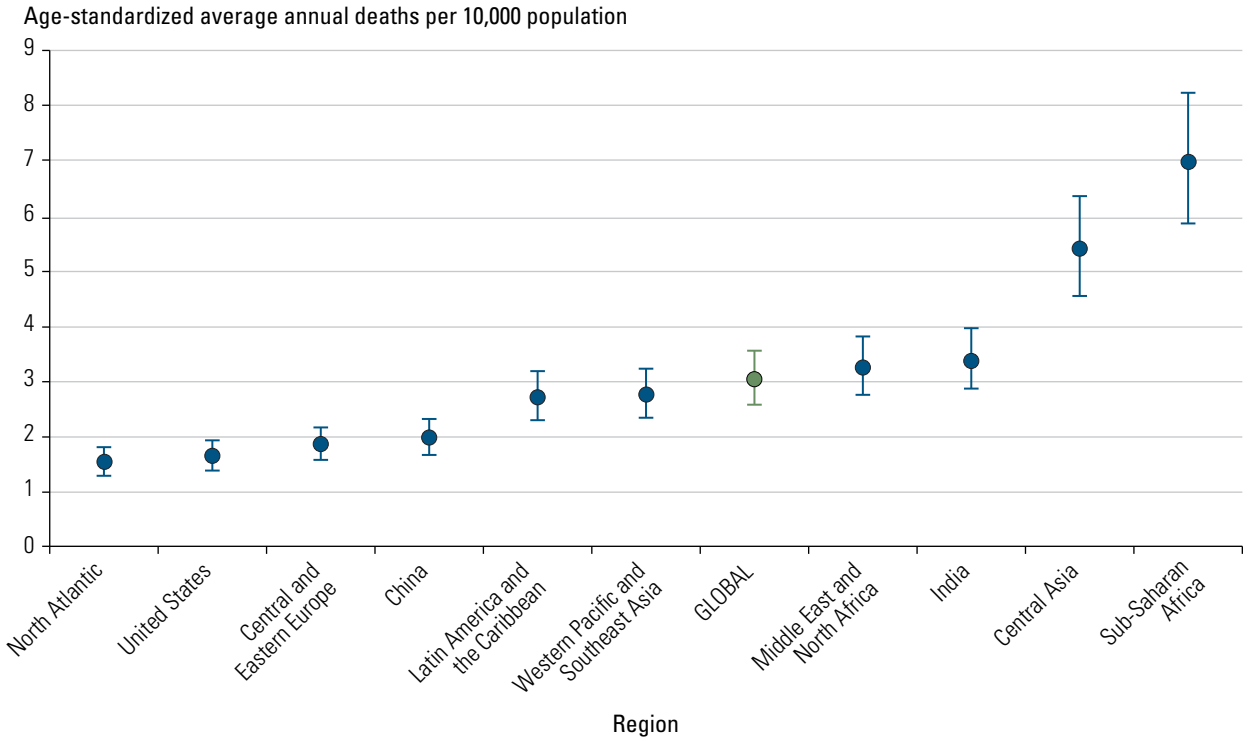
Table 2.7 Composition of AAL for Respiratory Event Catalog, by Event Severity and Event Frequency

AAL, by event severity		AAL, by event frequency	
Severity, millions of deaths globally	**Contribution to AAL, thousand (%)**	**Frequency indicated by return period, years**	**Contribution to AAL, thousand (%)**
200+	450 (18)	≤ 10	0.23 (0.01)
100–200	670 (27)	10–35	310 (13)
50–100	560 (23)	35–100	720 (29)
8–50	720 (29)	100–200	440 (18)
< 8	77 (3.1)	200+	1,000 (40)
Total	2,500 (100)	Total	2,500 (100)

Source: Ginkgo Biosecurity simulations.

Note: AAL = average annual loss.

Figure 2.4 Age-Standardized Average Annual Respiratory Disease Deaths, by Region, Based on Respiratory Event Catalog



Source: Original figure created for this publication, based on Ginkgo Biosecurity simulations and World Health Organization 2000–25 Standard Population (Ahmad et al. 2001).

Note: For details on regional groupings, refer to map 2.1 and annex 2B. The dots depict the point estimates, and the lines depict the 95 percent confidence intervals.

Table 2.8 Average Annual Deaths, by Region, Based on Respiratory Event Catalog

Region	Standardized average annual deaths per 10,000[a]	Average annual deaths per 10,000 population	Average annual deaths (thousand)
Global	3.0	3.2	2,500
Central and Eastern Europe	1.9	2.5	82
Central Asia	5.4	4.4	160
China	2.0	2.4	340
India	3.4	3.2	450
Latin America and the Caribbean	2.7	2.8	180
Middle East and North Africa	3.3	3.0	160
North Atlantic	1.5	2.3	100
Sub-Saharan Africa	7.0	5.0	580
United States	1.7	2.2	71
Western Pacific and Southeast Asia	2.8	3.0	340

Source: Ginkgo Biosecurity simulations.

Note: For details on regional groupings, refer to map 2.1 and annex 2B.

a. Based on World Health Organization 2000–25 Standard Population (Ahmad et al. 2001).

At first glance, the findings of higher expected mortality in Sub-Saharan Africa may appear inconsistent with the relatively low levels of reported mortality from the COVID-19 pandemic in that region, as compared to others. Notably, the ratio of the age-standardized AAL between Sub-Saharan Africa and the North Atlantic region as derived from table 2.8 is roughly 5:1. This ratio contradicts patterns of estimated excess mortality during the COVID-19 pandemic (table 2.2), which show higher mortality levels in the North Atlantic compared to Sub-Saharan Africa.

Multiple factors likely contribute to this apparent discrepancy. First, evidence suggests significant underreporting in the official statistics—more so in Sub-Saharan Africa than in the North Atlantic region. Estimates that draw on seroprevalence data to estimate mortality while correcting for underreporting find a higher mortality burden for Sub-Saharan Africa (Kogan et al. 2023). Second, the age distribution of deaths is likely to play a role. Comparative mortality ratios show a much higher mortality burden for Sub-Saharan Africa, especially when accounting for the region's younger age distribution (Ledesma et al. 2023). Note that this factor could be somewhat specific to COVID-19; a future respiratory pandemic could have a different pattern, potentially leading to a different spread in future expected losses. Third, mortality displacement may play a role. The following subsection discusses both age effects and mortality displacement.

Respiratory Mortality by Age Group

AAL results by age group are available in the respiratory model event catalog. Figure 2.5 shows a graph of the global normalized average annual deaths per 10,000 population by age group for respiratory pandemics. Table 2.9 contains the graphed values, including median and 95 percent CIs for each age group. These results show

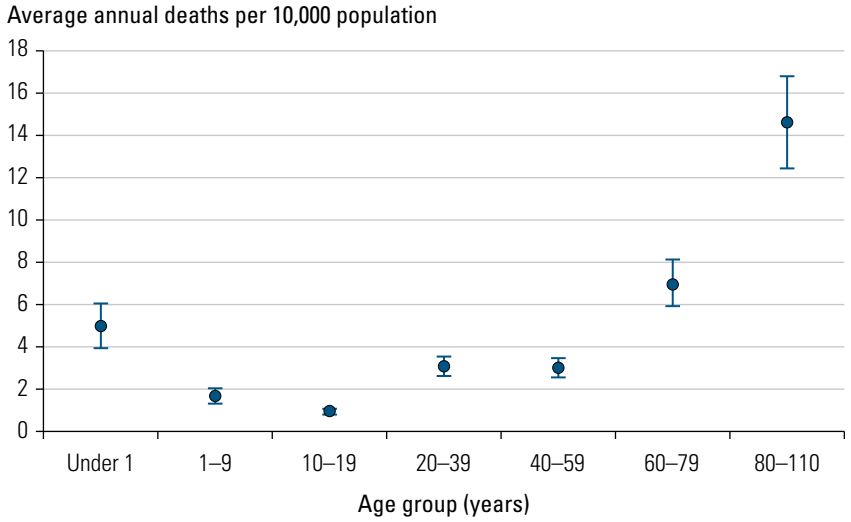
that members of the oldest two population groups are most likely to die during a respiratory pandemic, followed by the youngest in the population. The overall mortality rates exhibit a slight W-shaped pattern (Morens, Taubenberger, and Fauci 2021), but respiratory diseases can exhibit a number of different mortality patterns (for example, U or J). Although not well understood, the determinants of this pattern may be related to immunity patterns in the population (van Wijhe et al. 2018).

Increased mortality, especially in older age groups, can lead to what is known as mortality displacement, or the "harvesting effect." Such a situation involves a compensatory decrease in mortality after a pandemic, because the individuals who died in the pandemic would have been likely to die whether or not the pandemic occurred. This effect has been observed during influenza pandemics (Hoffman and Fox 2019) as well as the COVID-19 pandemic (Astengo et al. 2021).

Beyond the oldest and youngest individuals, who are at greatest mortality risk during a respiratory pandemic, the age groups having the next greatest risk are the 20- to 39-year-old and 40- to 59-year-old categories. The increased mortality for the 20–39 age category is especially concerning from the standpoint of fertility, along with economic losses, because this age category includes prime members of the labor force who would be conducting economically productive activities. Therefore, epidemics having a W-shaped mortality pattern are more likely to cause the greatest economic loss (Ma, Dushoff, and Earn 2011).

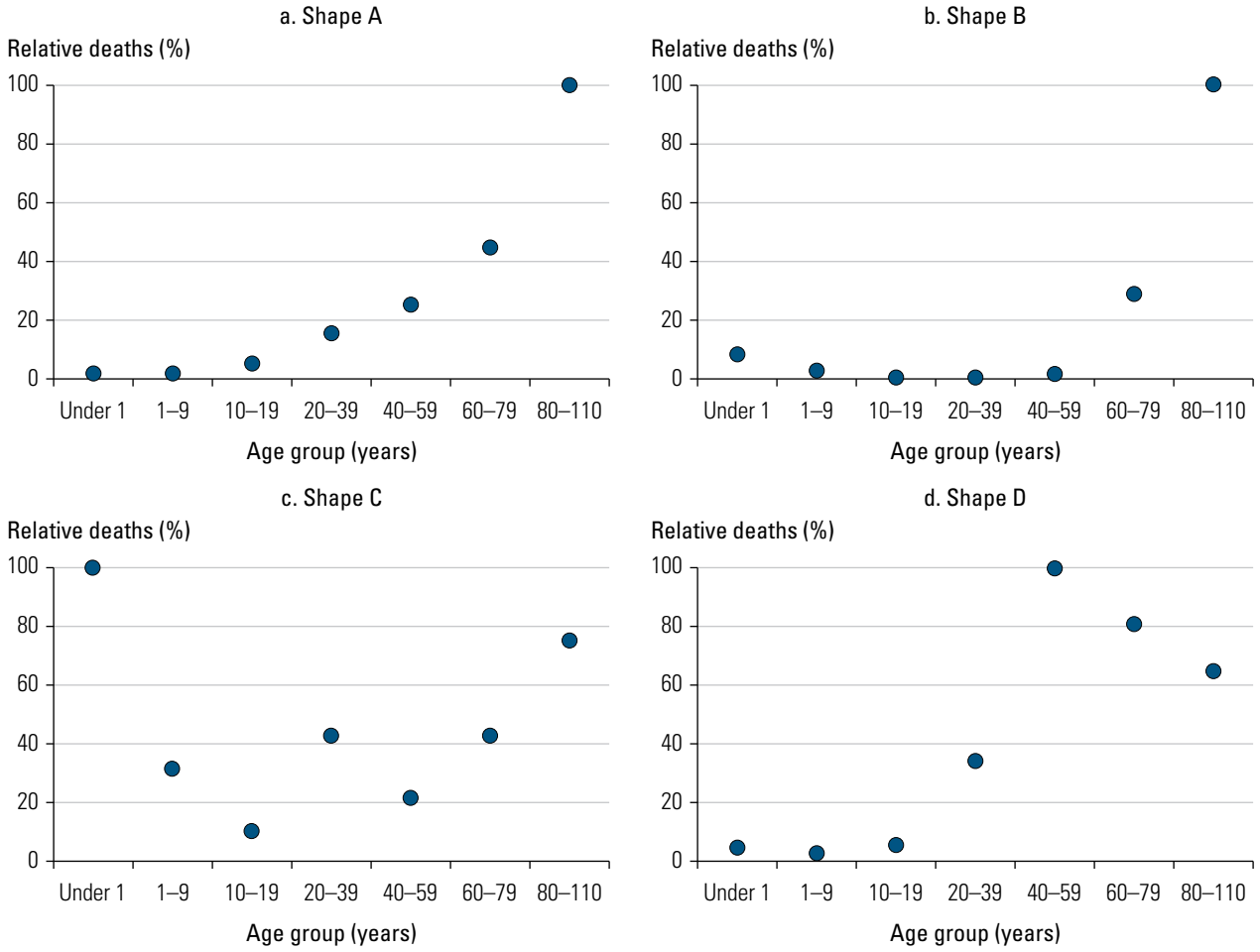
Although these results are averaged over the entire set of simulations, the age distribution can take many different forms for any single epidemic. These forms may differ from distributions observed in previous epidemics. For illustrative examples of various age distributions, refer to figure 2.6.

Figure 2.5 Average Annual Respiratory Disease Deaths, by Age Group, Based on Respiratory Event Catalog



Source: Original figure created for this publication, based on Ginkgo Biosecurity simulations.
Note: The dots depict the point estimates, and the lines depict the 95 percent confidence intervals.

Figure 2.6 Age Shapes of Respiratory Disease



Source: Original figure created for this publication.

Note: Relative deaths represent the percent of normalized deaths in an age category compared to the age category with the highest number of normalized deaths. These are illustrative examples of how pandemics could have varying levels of severity in different age groups, which could be related, for example, to pathogen characteristics, immunity levels in the affected populations, or differing contact patterns.

Table 2.9 Global Average Annual Deaths, by Age Group, Based on Respiratory Event Catalog

Age group (years)	Average annual deaths per 10,000 population in that age group	Average annual deaths in that age group (thousand)
Under 1	5.0	66
1–9	1.6	200
10–19	0.89	110
20–39	3.0	710
40–59	3.0	530
60–79	6.9	620
80–110	15	220
Global total	**3.2**	**2,500**

Source: Ginkgo Biosecurity simulations.

RESULTS: VIRAL HEMORRHAGIC FEVERS

VHFs, such as those caused by Ebola, Marburg, and Nipah viruses, can be fatal; and human-to-human transmission can spark large, sustained epidemics. However, the severity of disease, distinctive signs and symptoms after the prodromal phase, and direct contact transmission mechanism all reduce the likelihood of wide international spread. The analysis here focuses on Sub-Saharan Africa because it represents the vast majority of global VHF losses—approximately 72 percent. The next subsections present Sub-Saharan Africa regional estimates for the VHF event catalog, including AALs and EPs, along with estimates of mortality by age group.

VHF Mortality in Sub-Saharan Africa

The AAL from future VHF epidemics in Sub-Saharan Africa is estimated to be approximately 19,000 deaths (table 2.10); this includes years having 0 or very low levels of loss. This number represents a small fraction of expected losses in comparison to respiratory pandemics. The EPF for VHFs exhibits a skewed distribution, albeit less skewed than the heavy-tailed loss distribution for respiratory diseases (figure 2.7 and table 2.11).

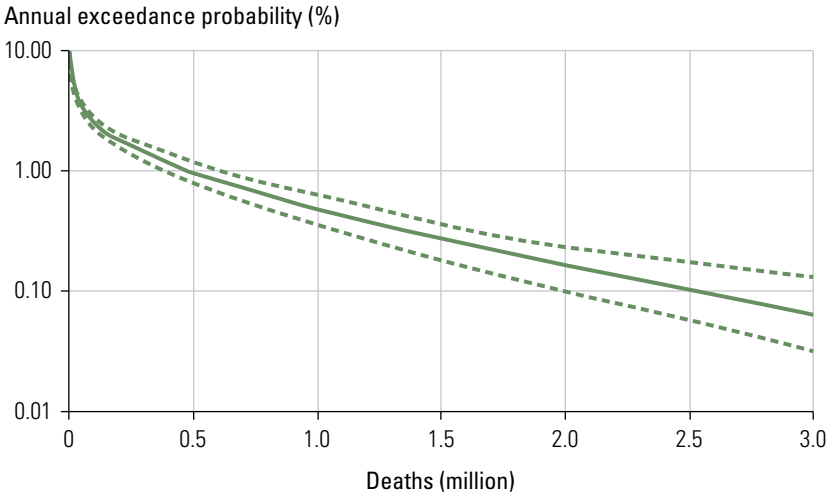
Table 2.10 Sub-Saharan Africa Average Annual Deaths Based on VHF Event Catalog

	Average annual deaths	
	Per 10,000 population	**Counts (thousand)**
VHFs	0.17	19

Source: Ginkgo Biosecurity simulations.

Note: VHF = viral hemorrhagic fever.

Figure 2.7 Viral Hemorrhagic Fever Exceedance Probability Function, Sub-Saharan Africa, Based on VHF Event Catalog



Source: Original figure created for this publication.

Note: The solid line depicts the point estimates, and the dashed lines depict the 95 percent confidence interval; VHF = viral hemorrhagic fever.

Table 2.11 Sub-Saharan Africa Deaths at Selected Exceedance Probability Points Based on VHF Event Catalog

Return period, years	Exceedance probability	Deaths per 10,000 population (95% CI)	Death counts, thousand (95% CI)
5	0.20000	0.01 (0.01, 0.01)	1.3 (1.2, 1.4)
10	0.10000	0.05 (0.05, 0.06)	6.3 (5.6, 7.1)
20	0.05000	0.24 (0.21, 0.28)	28 (24, 33)
35	0.02857	0.69 (0.59, 0.85)	80 (68, 98)
50	0.02000	1.4 (1.1, 1.8)	160 (130, 210)
100	0.01000	4.2 (3.3, 5.3)	480 (380, 610)
200	0.00500	8.4 (6.7, 11)	970 (770, 1,200)
333	0.00300	12 (9.6, 15)	1,400 (1,100, 1,700)
500	0.00200	16 (13, 20)	1,800 (1,400, 2,300)
667	0.00150	18 (14, 24)	2,100 (1,600, 2,800)
1,000	0.00100	22 (17, 30)	2,500 (2,000, 3,400)

Source: Ginkgo Biosecurity simulations.

Note: CI = confidence interval; VHF = viral hemorrhagic fever.

EPF estimates generated for this chapter suggest that outbreaks such as the Ebola virus disease epidemics in West Africa (2014) and North Kivu (2018 and 2021) are not aberrant events but instead reflect the risk profile of the region. The modeling framework here produces simulated events on the scale and duration of these events, along with events much larger than historically observed. The model results suggest that larger VHF epidemics are more likely to occur than might be assumed if one derives risk estimates based on historical data alone (box 2.2). Furthermore, the frequency and severity of VHF epidemics in Sub-Saharan Africa have increased in recent years (Stephens et al. 2022); if this trend continues, the risk of VHF events in Sub-Saharan Africa will increase even more over time.

As shown in table 2.12, a VHF epidemic causing approximately 10,000 deaths has an estimated 8 percent annual probability of occurrence; viewed over a 10-year period, the risk that such an event will occur is roughly 57 percent. An event five times that magnitude, causing 50,000 deaths within Sub-Saharan Africa, has a roughly 3.7 percent annual probability. Such an event lies outside the range of historical experience and appears improbable given the small annual probability; however, viewed over a 10-year time period, it has a 31 percent probability of occurrence. Over a 25-year period, this probability of occurrence increases to 61 percent. Refer to table 2C.2 in annex 2C for results of sensitivity testing around trend assumptions of future risk.

In the VHF model event catalog for Sub-Saharan Africa, total event sizes in death counts are smaller in magnitude than the respiratory catalog. Even so, about 2.5 percent of the events in the VHF model event catalog have at least 100,000 deaths in Sub-Saharan Africa, whereas nearly 50 percent of all deaths in the catalog are from events having 1 million deaths or more in Sub-Saharan Africa (figure 2.8).

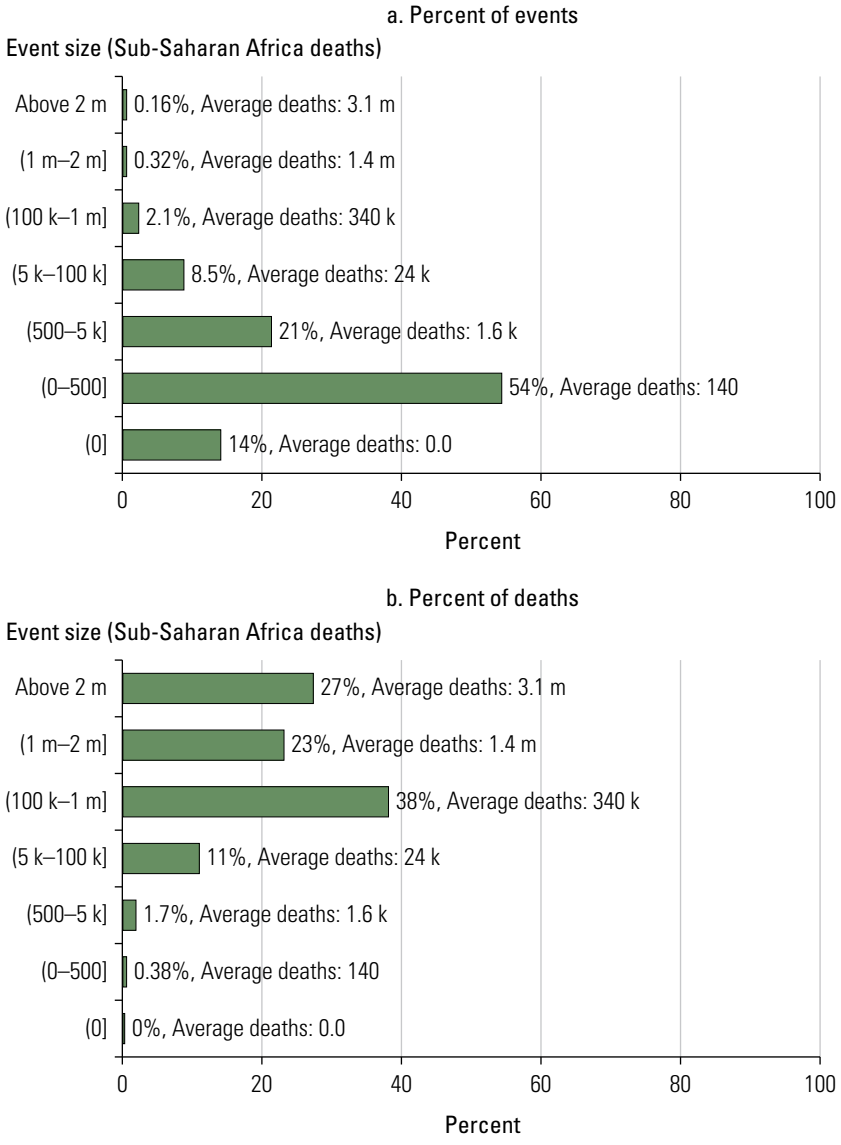
Table 2.12 Annual, 5-Year, 10-Year, and 25-Year EP Estimates for Selected Sub-Saharan Africa Event Sizes Based on VHF Event Catalog

Deaths	Annual EP (%)	5-year EP (%)	10-year EP (%)	25-year EP (%)
10,000	8.1	34	57	88
50,000	3.7	17	31	61
100,000	2.6	12	23	48

Source: Ginkgo Biosecurity simulations.

Note: EP = exceedance probability; VHF = viral hemorrhagic fever.

Figure 2.8 VHF Event Catalog Composition: Simulated Event Sizes and Contribution to Expected Losses



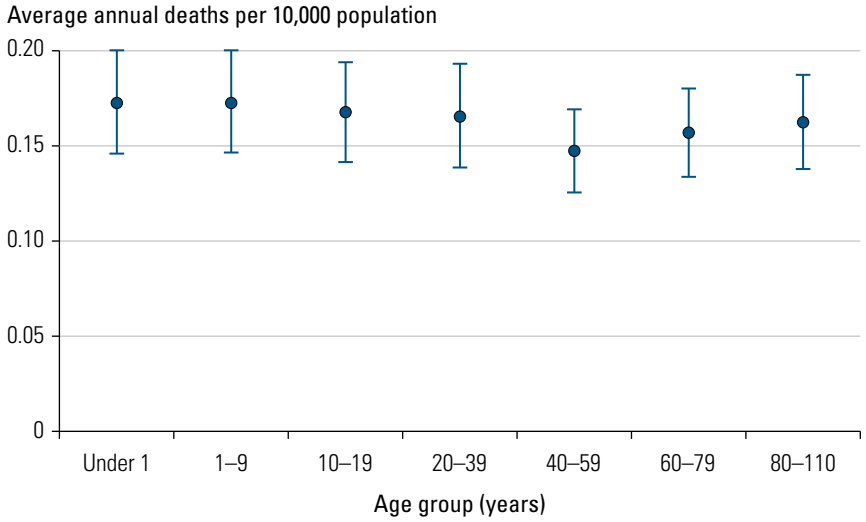
Source: Original figure created for this publication.

Note: The parentheses and brackets notation follows the international standard ISO 80000-2:2019(en) Quantities and units—Part 2, which conveys the following meaning. The "(" indicates the range is exclusive of the number, while "[" and "]" indicate the range is inclusive; k = thousand; m = million; VHF = viral hemorrhagic fever.

VHF Mortality by Age Group

AAL was calculated for each of the modeled age groups. In contrast to the respiratory disease catalog, the normalized average annual deaths per 10,000 population varies considerably less across age groups. Figure 2.9 contains a graph of the normalized average annual deaths per 10,000 population for the VHF modeled event catalog in Sub-Saharan Africa. Table 2.13 presents the graphed values. This analysis suggests that VHFs are more universally fatal, with mortality less differentiated by age than as seen with respiratory diseases (Garske et al. 2017; Rosello et al. 2015).

Figure 2.9 Average Annual Viral Hemorrhagic Fever Deaths, by Age Group, Based on VHF Event Catalog



Source: Original figure created for this publication.

Note: The dots depict the point estimates, and the lines depict the 95 percent confidence intervals; VHF = viral hemorrhagic fever.

Table 2.13 Sub-Saharan Africa Average Annual Deaths, by Age Group, Based on VHF Event Catalog

Age group (years)	Average annual deaths per 10,000 population in that age group	Average annual deaths in that age group (thousand)
Under 1	0.17	0.66
1–9	0.17	5.3
10–19	0.17	4.4
20–39	0.17	5.5
40–59	0.15	2.2
60–79	0.16	0.80
80–110	0.16	0.07
Sub-Saharan Africa Total	**0.17**	**19**

Source: Ginkgo Biosecurity simulations.

Note: VHF = viral hemorrhagic fever.

DISCUSSION

The simulation-based results presented in this chapter demonstrate the scale of the risk posed by pathogens of epidemic potential. The estimated global AAL of 2.5 million deaths represents a larger and more comprehensive accounting of the risk than was presented in *DCP3* (Fan, Jamison, and Summers 2017; Madhav et al. 2017). The view of risk presented here—particularly the focus on losses in terms of deaths—also clearly represents a lower-bound estimate of total potential impact because it does not include other sources of loss to human health and livelihoods (for example, infections, hospitalizations, long-term sequelae, economic shocks, impacts on education, and societal disruption), nor—as noted earlier—does it include all sources of epidemic risk, such as vector-borne pathogens, bacterial infections, and viral threats presently unknown to science.

The results also suggest that, among the diseases modeled, respiratory diseases are the dominant driver of epidemic risk, with VHFs representing a relatively modest global risk in terms of expected deaths. Although deadlier on an individual level, VHFs are less prone to spread than respiratory diseases. Their risk is not negligible, however, especially in Sub-Saharan Africa, and merits attention because of the direct and indirect impacts of these events on lives and livelihoods (Sochas, Channon, and Nam 2017).

Magnitude of Epidemic and Pandemic Risk

Effective priority setting in global health requires the comparison of disparate burdens and risks, some of which operate on different timescales. As such, it may be helpful to understand how the mortality estimates here compare to other risks. It might seem intuitive to compare epidemic AAL to the annual mortality burden caused by endemic diseases, because both represent average deaths per year. For example, the average annual deaths estimated here for respiratory epidemics is comparable in magnitude to the annual number of deaths caused by routinely occurring endemic lower respiratory infections—approximately 2.4 million deaths (Troeger et al. 2018). When comparing such estimates, however, it is important to keep in mind the very different underlying patterns leading to these averages. Whereas the average annual deaths from endemic diseases are made up of moderate levels of loss that occur regularly, the epidemic AAL represents much larger spikes in losses that occur sporadically, punctuating stretches of nonepidemic years. Mortality spikes caused by low-frequency, high-severity events are potentially more economically disruptive than regularly occurring endemic disease, suggesting that, even when AALs may be similar between both types of diseases, planning efforts for high-impact epidemics should at least be equal to, if not greater than, endemic diseases.

The model results also show that tail risk cannot be ignored. Low-frequency, high-severity events—the tail in the results for this chapter—heavily drive expected deaths. It is all too easy to unconsciously discount the risk that the tail represents. The underrepresentation of extreme events in small sample sizes can lead policy

makers to underweight their probability, especially when relying on a limited and biased historical data set (Slovic and Weber 2011). Moreover, because of cognitive biases that draw attention to the frequency component of risk rather than the joint product of frequency *and* severity, the low annual probability of such extreme events tends to cause policy makers to round this probability down toward zero.

To compensate for this discounting bias, this chapter has presented risk estimates for key points on the EPFs in terms of probability of occurrence over the next 5, 10, and 25 years. The results demonstrate how seemingly minute risks are far more substantial when viewed over a somewhat longer time horizon but still relevant in terms of policy making and budgeting. Over a 10-year view, an event on the scale of COVID-19 has a roughly 25 percent probability of occurrence; over the next 25 years, such an event has a likelihood roughly equivalent to a coin toss. These estimates demonstrate that future epidemic risk is more substantial than commonly believed and that severe events are likely to occur much more frequently than once in a century.

Prevention, Mitigation, and Response Strategies

The estimates presented in this chapter do not, on their face, provide much cause for optimism. The expected losses from epidemic risk are enormous, and the results point to the considerable potential for pandemics that dwarf COVID-19 in terms of human impacts. Expectations can change, however. The risk estimates presented are not immutable. Risk could increase if the global community does not take meaningful steps to address the underlying drivers of risk. Conversely, risk can be reduced through investments in prevention (for example, spillover risk reduction), surveillance, preparedness, and response, which can be achieved through investments from basic necessities to technological innovations.

General investments in health system strengthening can significantly reduce epidemic losses, including those caused by respiratory diseases and VHFs. Because severe events occur sporadically, it is difficult to compare the benefits of improving preparedness between crises: other important determinants, such as technologies to produce medical countermeasures, may also have changed over time. These investments can easily appear to be wasted on threats that do not materialize, but investments to prepare for severe epidemics can also support effective responses to smaller events and other infectious disease risks, even in interpandemic periods. Such general investments having far-reaching benefits include improved laboratory capacity for rapid detection and confirmation of infectious disease threats (Wacharapluesadee et al. 2020), and border monitoring programs to track the importation risk of high-consequence pathogens (Wegrzyn et al. 2022). These improvements can also keep surveillance and response infrastructure "warm"—that is, in continuous operational performance so it may persist in a constant state of readiness. Surveillance and response systems need to operate continuously, both between and during epidemics, so that they can be constantly used and stress-tested, and also so they can detect epidemics in the earliest days of their spark and

emergence, because early action has the potential for greatest impact. Ultimately, building these capacities will provide the greatest opportunity to stop an outbreak before it becomes an epidemic or a globally catastrophic pandemic.

Localized outbreaks and smaller epidemics provide additional risk mitigation possibilities. For example, because of the more localized nature of VHFs, the spark location is more influential to the overall mortality for VHFs than for respiratory diseases (Madhav et al. 2020), and potential spark locations are good candidates for spillover reduction efforts. Additionally, for VHFs, interventions often are implemented with a more localized approach than respiratory diseases. For example, health officials have employed ring vaccination, in contrast to mass vaccination, with *Zaire ebolavirus* vaccines and Marburg vaccine candidates (Cross et al. 2022). Furthermore, localized epidemics are more geographically constrained, leading to greater likelihood for international cooperation because neighboring countries and the international community can spare more resources—such as workforce, supplies, and financial assistance—for the affected country, which can greatly improve outcomes.

Importance of a Risk-Informed Lens

Although it is impossible to predict the timing and magnitude of the next epidemic, risk modeling can provide informed views of the potential frequency and severity of future epidemics. The key question is what exactly the world should be preparing for. Effectively preparing for an event as severe as the 1918 influenza pandemic could require very different strategies and levels of investment than would be needed, for example, to prepare for a COVID-19-level event. Although it is infeasible and resource-inefficient to plan for every epidemic that could possibly occur, plans should be flexible and adaptable, to handle a wide range of possibilities. Careful consideration of the full range of potential epidemic scenarios—by guiding discussions about the types of surveillance and response systems that must be built, and the level of financing required—can ensure that preparedness and response plans are commensurate with the level of risk. A risk-informed approach can help governments make better decisions around preparedness, ensuring that the world is ready for the next pandemic while making efficient use of limited resources.

Decision-makers traditionally have used a risk-informed analysis framework to prepare for other hazards besides epidemics. For example, in the design of wind loads for bridges, engineers often use a 2 percent annual probability (50-year return period) as a guideline (Garlich et al. 2015). Similarly, engineers may build urban road drainage systems to handle the flood risks from a precipitation event with a 2 percent annual probability (50-year return period) but may build high-risk levees to withstand floods up to a 0.1 percent annual probability (1,000-year return period) because of the catastrophic consequences of failure (Ponce 2008). Discussion of the suitability of these particular risk tolerance thresholds, and whether they should be adopted in planning for epidemic and pandemic risk, is important for risk-informed

policy making and effective resource allocation, but is beyond the scope of this chapter. Further discussion may be found elsewhere (for example, refer to Strouth et al. 2019).

Planners and decision-makers can likewise develop risk-informed epidemic preparedness, mitigation, and response plans, relying on EPFs to provide necessary metrics. In practice, depending on country resources and risk tolerance, decision-makers would work to a preparedness target for their country—for example, to be ready for an epidemic with a 5 percent annual probability (20-year return period). Preparedness at this level would imply that a country could effectively respond to an epidemic of that magnitude and bring it under containment. Countries could determine their acceptable risk thresholds for epidemics by using existing frameworks such as the precautionary principle or as low as reasonably practicable (Pike, Khan, and Amyotte 2020).

To meet these risk thresholds, risk models can provide further details to help design and calibrate specific investments. Risk modeling shows that transmissibility and case fatality ratio greatly influence overall epidemic severity for both respiratory pathogens and VHFs. Thus, the intervention measures with the most impact for reducing mortality should target investments that reduce these factors. Toward this aim, risk modeling can be used to estimate stockpile sizes and resource needs for personal protective equipment, diagnostic tests, vaccine doses, antiviral drugs, and other therapeutics, as well as the effects of intervention timing and the costs associated with implementing these measures. Risk models can also help countries develop financing strategies, including risk transfer mechanisms, to offload portions of risk and response that are beyond their immediate budgetary capacity (Asian Development Bank 2022; Madhav et al. 2020).

Larger epidemics require higher-level planning and may need to include provisions for regional cooperation to have the greatest chance at success. For example, developing regional vaccine manufacturing facilities may be a cost-effective and politically viable approach to building surge production capacity (Jha et al. 2021).

International standards for preparedness could also take a risk-informed approach, such as by setting benchmarks for risk tolerance and minimum preparedness levels to counter the potential for a "weakest link" effect. Such a model could, for example, require that all countries be prepared to respond effectively to a respiratory event at least at the 5 percent annual probability level. This type of requirement could augment assessments such as the Joint External Evaluation, which sets standards for the prevention, preparedness, and response capacities that countries must have in place, but does not specify what level of risk mitigation or reduction those capacities can achieve. Countries should strive to take a data-driven and modeling-informed approach to assess their level of risk and risk tolerance, along with their country context, to set the appropriate thresholds for their own country following a common standard.

Requiring that countries meet a common standard for risk tolerance and preparedness would also require sustained financing to meet and maintain the necessary capacities. Many low- and middle-income countries face challenges in financing preparedness and response capacities because of budgeting constraints and competing health system priorities, such as high-burden endemic diseases. However, early detection and mitigation of pathogens with epidemic and pandemic potential represent a global public good that protects the health, national security, and economic prosperity of all countries. Given the scale of the risk, the G20 High Level Independent Panel on Financing the Global Commons for Pandemic Preparedness and Response proposed a dramatic scale-up of financing, including substantial aid for low- and middle-income countries (Shanmugaratnam et al. 2021), which would allow these countries to meet minimum preparedness and response thresholds. One of the primary barriers to effective, and effectively scaled, collective action is uncertainty regarding the magnitude and timing of future pandemics. This type of uncertainty has the well-characterized problem of leading to market failure (Arrow 1963)—in this case, underinvestment in global public goods such as surveillance and response capacities.

A risk-informed view can also prevent policy makers from falling victim to recency bias and overcalibrating to historical experience. For years, historical influenza pandemics were the planning benchmark for pandemic preparedness (US Department of Health and Human Services 2005). The experience of the relatively mild 2009 influenza pandemic led some analysts to conclude that the global community had overplanned and overinvested (Low and McGeer 2010). That conclusion may have even fueled the complacency and neglect that led to shortcomings in the global COVID-19 response. As the most recent severe pandemic, COVID-19 will likely become a de facto planning benchmark. The modeling results presented here suggest that doing so would be short-sighted. Multiple pandemics have occurred over the past century, with varying characteristics and magnitudes. Extreme events modeling shows that a wider range of scenarios is possible and should be taken into consideration to limit the risk of strategic surprise (Fukuyama 2008). Furthermore, the model results in this chapter suggest, and historical experience corroborates, that events more severe than previous historical observations can and do occur. The 2014 West Africa Ebola epidemic, which exceeded deaths during prior Ebola outbreaks by two orders of magnitude, vividly illustrates this point.

The results presented in this chapter strongly suggest that epidemic risk is far more persistent and substantial than is commonly believed. The probability exists that an epidemic—or even a large pandemic—could start in any year. The results demonstrate the urgency and priority of action to mitigate the risk. Armed with this knowledge, the world can be ready for the next major pandemic, which, in all likelihood, will not wait 100 years to find us.

ACKNOWLEDGMENTS

This content was prepared for publication as this chapter in *Disease Control Priorities, Fourth Edition*, Volume 2, and as a background paper for the *Lancet* Commission on Investing in Health (Jamison et al., 2024).

The authors thank Ben Ash, Stefano Bertozzi, Matteo Chinazzi, Jason Euren, Mike Gahan, Mark Gallivan, Daniel Katz, Seri Lee, Melissa Lesh, Matthew McKnight, Kierste Miller, Ole F. Norheim, Chris Pardee, Ana Pastore y Piontti, Patrick Savage, Volodymyr Serhiyenko, Siddhanth Sharma, Vikram Sridharan, Cristina Stefan, Lawrence Summers, Swati Sureka, Alessandro Vespignani, and Qian Zhang for their valuable programmatic, technical, and editorial contributions. They also thank the participants of prior DCP4 meetings and convenings who provided valuable feedback on various iterations of the manuscript.

The authors gratefully acknowledge the University of Bergen Centre for Ethics and Priority Setting in Health and the Norwegian Agency for Development Cooperation (NORAD) (RAF-18/0009) for providing funding support. Certain supporting data and code are publicly available in the following repositories:

- Zoonotic disease data: https://github.com/concentricbyginkgo/zoonotic_spillover_trend
- Underreporting: https://github.com/metabiota-ameadows/underreporting
- COVID-19 data set: https://data.humdata.org/dataset/2019-novel-coronavirus-cases.

Other data and model code are considered commercial/proprietary and cannot be publicly released. Nita K. Madhav, Ben Oppenheim, Nicole Stephenson, Rinette Badker, Cathine Lam, and Amanda Meadows are or have been employed by Ginkgo Bioworks.

REFERENCES

Ahmad, O. B., C. Boschi-Pinto, A. D. Lopez, C. J. Murray, R. Lozano, and M. Inoue. 2001. "Age Standardization of Rates: A New WHO Standard." GPE Discussion Paper No. 31, World Health Organization, Geneva.

Arrow, K. J. 1963. "Uncertainty and the Welfare Economics of Medical Care." *The American Economic Review* 53 (5): 941–73.

Asian Development Bank. 2022. *Building Resilience to Future Outbreaks: Infectious Disease Risk Financing Solutions for the Central Asia Regional Economic Cooperation Region*. Manila, Asian Development Bank. http://dx.doi.org/10.22617/TCS220010-2.

Astengo, M., F. Tassinari, C. Paganino, S. Simonetti, D. Gallo, D. Amicizia, M. F. Piazza, et al. 2021. "Weight of Risk Factors for Mortality and Short-Term Mortality Displacement during the COVID-19 Pandemic." *Journal of Preventive Medicine and Hygiene* 62 (4): E864.

Badker, R., K. Miller, C. Pardee, B. Oppenheim, N. Stephenson, B. Ash, T. Philippsen, et al. 2021. "Challenges in Reported COVID-19 Data: Best Practices and Recommendations for Future Epidemics." *BMJ Global Health* 6 (5): e005542.

Baker, R. E., A. S. Mahmud, I. F. Miller, M. Rajeev, F. Rasambainarivo, B. L. Rice, S. Takahashi, et al. 2021. "Infectious Disease in an Era of Global Change." *Nature Reviews Microbiology* 20: 193–205.

Bargain, O., and U. Aminjonov. 2020. "Trust and Compliance to Public Health Policies in Times of COVID-19." *Journal of Public Economics* 192 (December): 104316.

Bennett, J. E., R. Dolin, and M. J. Blaser. 2019. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases E-book*. Elsevier Health Sciences. https://www.us.elsevierhealth.com/mandell-douglas-and-bennetts-principles-and-practice-of-infectious-diseases-9780323482554.html.

Carlson, C. J., G. F. Albery, C. Merow, C. H. Trisos, C. M. Zipfel, E. A. Eskew, K. J. Olival, et al. 2022. "Climate Change Increases Cross-Species Viral Transmission Risk." *Nature* 607 (7919): 555–62.

Cherry, J. D. 2004. "The Chronology of the 2002–2003 SARS Mini Pandemic." *Paediatric Respiratory Reviews* 5 (4): 262–69.

Cirillo, P., and N. N. Taleb. 2020. "Tail Risk of Contagious Diseases." *Nature Physics* 16 (6): 606–13.

Contreras, S., E. N. Iftekhar, and V. Priesemann. 2023. "From Emergency Response to Long-Term Management: The Many Faces of the Endemic State of COVID-19." *The Lancet Regional Health–Europe* 30: 100664.

Cross, R. W., I. M. Longini, S. Becker, K. Bok, D. Boucher, M. W. Carroll, J. V. Díaz, et al. 2022. "An Introduction to the Marburg Virus Vaccine Consortium, MARVAC." *PLOS Pathogens* 18 (10): e1010805.

Cruickshank, M., and R. Z. Shaban. 2020. "COVID-19: Lessons to be Learnt from a Once-in-a-Century Global Pandemic." *Journal of Clinical Nursing* 29 (21–22): 3901.

Diallo, M. S. K., M. Rabilloud, A. Ayouba, A. Touré, G. Thaurignac, C. Butel, C. Kpamou, et al. 2019. "Prevalence of Infection among Asymptomatic and Paucisymptomatic Contact Persons Exposed to Ebola Virus in Guinea: A Retrospective, Cross-Sectional Observational Study." *The Lancet Infectious Diseases* 19 (3): 308–16.

Embrechts, P., S. I. Resnick, and G. Samorodnitsky. 1999. "Extreme Value Theory as a Risk Management Tool." *North American Actuarial Journal* 3 (2): 30–41.

Fan, V. Y., D. Jamison, and L. H. Summers. 2017. "The Loss from Pandemic Influenza Risk." In *Disease Control Priorities: Improving Health and Reducing Poverty*, Vol. 9, edited by D. Jamison. Washington, DC: World Bank.

Farzanegan, M. R., and H. P. Hofmann. 2022. "A Matter of Trust? Political Trust and the COVID-19 Pandemic." *International Journal of Sociology* 52 (6): 476–99.

FEMA (US Federal Emergency Management Agency). 2016. "The 100 Year Flood Myth." FEMA, https://biotech.law.lsu.edu/blog/AGENCY-The-100-Year-Flood-Myth.pdf.

Fraser, C., S. Riley, R. M. Anderson, and N. M. Ferguson. 2004. "Factors That Make an Infectious Disease Outbreak Controllable." *Proceedings of the National Academy of Sciences of the United States of America* 101 (16): 6146–51.

Fukuyama, F. 2008. *Blindside: How to Anticipate Forcing Events and Wild Cards in Global Politics*. Rowman & Littlefield.

Garlich, M. J., T. H. Pechillo, J. M. Schneider, T. Helwig, M. A. O'Toole, S.-L. C. Kaderbek, M. A. Grubb, and J. Ashton. 2015. *Engineering for Structural Stability in Bridge Construction*. United States. Federal Highway Administration. Office of Bridge Technology.

Garske, T., A. Cori, A. Ariyarajah, I. M. Blake, I. Dorigatti, T. Eckmanns, C. Fraser, et al. 2017. "Heterogeneities in the Case Fatality Ratio in the West African Ebola Outbreak 2013–2016." *Phil. Trans. R. Soc. B* 372 (1721): 20160308.

Gates, B. 2020. "Responding to Covid-19—A Once-in-a-Century Pandemic?" *New England Journal of Medicine* 382 (18): 1677–79.

Glennon, E. E., F. L. Jephcott, O. Restif, and J. L. N. Wood. 2019. "Estimating Undetected Ebola Spillovers." *PLOS Neglected Tropical Diseases* 13 (6): e0007428.

Gomes, M. F. C., A. Pastore y Piontti, L. Rossi, D. Chao, I. Longini, M. E. Halloran, and A. Vespignani. 2014. "Assessing the International Spreading Risk Associated with the 2014 West African Ebola Outbreak." *PLOS Currents*. https://pmc.ncbi.nlm.nih.gov/articles/PMC4169359/.

Guterres, A. 2020. "All Hands on Deck to Fight a Once-in-a-Lifetime Pandemic." *The United Nations COVID-19 Response,* April 2, 2020. https://www.un.org/en/un-coronavirus-communications-team/all-hands-deck-fight-once-lifetime-pandemic.

Han, B. A., A. M. Kramer, and J. M. Drake. 2016. "Global Patterns of Zoonotic Disease in Mammals." *Trends in Parasitology* 32 (7): 565–77.

Hoffman, B. L., and D. P. Fox. 2019. "The 1918–1920 H1N1 Influenza A Pandemic in Kansas and Missouri: Mortality Patterns and Evidence of Harvesting." *Transactions of the Kansas Academy of Science* 122 (3–4): 173–92.

Jamison, D. T., L. H. Summers, G. Alleyne, K. J. Arrow, S. Berkley, A. Binagwaho, F. Bustreo. 2013. "Global Health 2035: A World Converging within a Generation." *The Lancet* 382 (9908): 1898–955.

Jamison, D. T., L. H. Summers, A. Y. Chang, O. Karlsson, W. Mao, O. F. Norheim, O. Ogbuoji, et al. 2024. "Global Health 2050: The Path to Halving Premature Death by Mid-Century. *The Lancet* 404 (10462): 1561–1614. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)01439-9/fulltext.

Jha, P., D. T. Jamison, D. A. Watkins, and J. Bell. 2021. "A Global Compact to Counter Vaccine Nationalism." *The Lancet* 397 (10289): 2046–47.

Johnson, N. P. A. S., and J. Mueller. 2002. "Updating the Accounts: Global Mortality of the 1918–1920 'Spanish' Influenza Pandemic." *Bulletin of the History of Medicine* 76 (1): 105–15.

Jombart, T., C. I. Jarvis, S. Mesfin, N. Tabal, M. Mossoko, L. M. Mpia, A. A. Abedi, et al. 2020. "The Cost of Insecurity: From Flare-Up to Control of a Major Ebola Virus Disease Hotspot during the Outbreak in the Democratic Republic of the Congo, 2019." *Eurosurveillance* 25 (2): 1900735.

Jones, B. A., D. Grace, R. Kock, S. Alonso, J. Rushton, M. Y. Said, D. McKeever, et al. 2013. "Zoonosis Emergence Linked to Agricultural Intensification and Environmental Change." *Proceedings of the National Academy of Sciences* 110 (21): 8399–404.

Jones, K. E., N. G. Patel, M. A. Levy, A. Storeygard, D. Balk, J. L. Gittleman, and P. Daszak. 2008. "Global Trends in Emerging Infectious Diseases." *Nature* 451 (7181): 990–93.

Kaplan, S., and B. J. Garrick. 1981. "On the Quantitative Definition of Risk." *Risk Analysis* 1 (1): 11–27.

Kogan, N. E., S. Gantt, D. Swerdlow, C. Viboud, M. Semakula, M. Lipsitch, and M. Santillana. 2023. "Leveraging Serosurveillance and Postmortem Surveillance to Quantify the Impact of Coronavirus Disease 2019 in Africa." *Clinical Infectious Diseases* 76 (3): 424–32.

Kozlowski, R. T., and S. B. Mathewson. 1995. "Measuring and Managing Catastrophe Risk." *Journal of Actuarial Practice* 3: 211–32. https://digitalcommons.unl.edu/joap/132/.

Ledesma, J. R., C. R. Isaac, S. F. Dowell, D. L. Blazes, G. V. Essix, K. Budeski, J. Bell, and J. B. Nuzzo. 2023. "Evaluation of the Global Health Security Index as a Predictor of COVID-19 Excess Mortality Standardised for Under-Reporting and Age Structure." *BMJ Global Health* 8 (7): e012203.

Lempert, R. J., and P. C. Light. 2009. "Evaluating and Implementing Long-Term Decisions." *The RAND Frederick S. Pardee Center*, 11.

Low, D. E., and A. McGeer. 2010. "Pandemic (H1N1) 2009: Assessing the Response." *CMAJ* 182 (17): 1874–78.

Ma, J., J. Dushoff, and D. J. Earn. 2011. "Age-Specific Mortality Risk from Pandemic Influenza." *Journal of Theoretical Biology* 288: 29–34.

Madhav, N., H. K. Bosa, R. D. Agyarko, N. Stephenson, K. Miller, M. Gallivan, C. Lam, et al. 2020. "Development of a Risk Modeling Approach to Enhance the Effectiveness of Epidemic Preparedness, Response, and Financing Strategies in African Countries." *International Journal of Infectious Diseases* 101: 212–13.

Madhav, N., B. Oppenheim, M. Gallivan, P. Mulembakani, E. Rubin, and N. Wolfe. 2017. "Pandemics: Risks, Impacts, and Mitigation." In *Disease Control Priorities* (third edition), Volume 9, *Improving Health and Reducing Poverty*, edited by D. T. Jamison, H. Gelband,

S. Horton, P. Jha, R. Laxminarayan, C. N. Mock, and R. Nugent. Washington, DC: World Bank. http://www.ncbi.nlm.nih.gov/books/NBK525302/.

Madhav, N., N. Stephenson, and B. Oppenheim. 2021. "Multipathogen Event Catalogs Technical Note." World Bank, Washington, DC. https://documents1.worldbank.org/curated/en/181791625232959415/pdf/Multi-Pathogen-Event-Catalogs-Technical-Note.pdf.

Marani, M., G. G. Katul, W. K. Pan, and A. J. Parolari. 2021. "Intensity and Frequency of Extreme Novel Epidemics." *Proceedings of the National Academy of Sciences* 118 (35): e2105482118. https://doi.org/10.1073/pnas.2105482118.

Meadows, A. J., B. Oppenheim, J. Guerrero, B. Ash, R. Badker, C. K. Lam, C. Pardee, et al. 2022. "Infectious Disease Underreporting Is Predicted by Country-Level Preparedness, Politics, and Pathogen Severity." *Health Security* 20 (4): 331–38.

Meadows, A. J., N. Stephenson, N. K. Madhav, and B. Oppenheim. 2023. "Historical Trends Demonstrate a Pattern of Increasingly Frequent and Severe Epidemics of High-Consequence Zoonotic Viruses." *BMJ Global Health* 8 (11): e012026.

Meslé, M. M., R. Vivancos, I. M. Hall, R. M. Christley, S. Leach, and J. M. Read. 2022. "Estimating the Potential for Global Dissemination of Pandemic Pathogens Using the Global Airline Network and Healthcare Development Indices." *Scientific Reports* 12 (1): 3070a.

Morens, D. M., J. K. Taubenberger, and A. S. Fauci. 2021. "A Centenary Tale of Two Pandemics: The 1918 Influenza Pandemic and COVID-19, Part I." *American Journal of Public Health* 111 (6): 1086–94.

Morens, D. M., J. K. Taubenberger, G. K., Folkers, and A. S. Fauci. 2010. "Pandemic Influenza's 500th Anniversary." *Clinical Infectious Diseases* 51 (12): 1442–44.

Msemburi, W., A. Karlinsky, V. Knutson, S. Aleshin-Guendel, S. Chatterji, and J. Wakefield. 2023. "The WHO Estimates of Excess Mortality Associated with the COVID-19 Pandemic." *Nature* 613 (7942): 130–37.

Nelson, K. E., and C. M. Williams. 2014. *Infectious Disease Epidemiology: Theory and Practice*. Jones & Bartlett Publishers.

Olival, K. J., P. R. Hosseini, C. Zambrana-Torrelio, N. Ross, T. L. Bogich, and P. Daszak. 2017. "Host and Viral Traits Predict Zoonotic Spillover from Mammals." *Nature* 546 (7660): 646–50.

Pike, H., F. Khan, and P. Amyotte. 2020. "Precautionary Principle (PP) versus As Low As Reasonably Practicable (ALARP): Which One to Use and When." *Process Safety and Environmental Protection* 137: 158–68.

Ponce, V. M. 2008. "Q & A on the Return Period to Be Used for Design." San Diego State University, CA. https://ponce.sdsu.edu/return_period.html.

Porta, M. 2014. *A Dictionary of Epidemiology*. Oxford University Press.

Price-Smith, A. T. 2001. *The Health of Nations: Infectious Disease, Environmental Change, and Their Effects on National Security and Development*. MIT Press.

Resolve to Save Lives. 2021. *Epidemics That Didn't Happen*. New York: Resolve to Save Lives. https://preventepidemics.org/epidemics-that-didnt-happen-2021/.

Rosello, A., M. Mossoko, S. Flasche, A. J. V. Hoek, P. Mbala, A. Camacho, S. Funk, et al. 2015. "Ebola Virus Disease in the Democratic Republic of the Congo, 1976–2014." *ELife* 4: e09015.

Sands, P., C. Mundaca-Shah, and V. J. Dzau. 2016. "The Neglected Dimension of Global Security—A Framework for Countering Infectious-Disease Crises." *New England Journal of Medicine* 374 (13)" 1281–87.

Shanmugaratnam, T., L. Summers, N. Okonjo-Iweala, A. Botin, M. El-Erian, J. Frenkel, R. Grynspan, et al. 2021. *A Global Deal for Our Pandemic Age*. Report of the G20 High Level Independent Panel on Financing the Global Commons for Pandemic Preparedness and Response. Pandemic Financing. https://pandemic-financing.org/wp-content/uploads/2021/07/G20-HLIP-Report.pdf.

Sirleaf, E. J., and H. Clark. 2021. "Report of the Independent Panel for Pandemic Preparedness and Response: Making COVID-19 the Last Pandemic." *The Lancet* 398 (10295): 101–3.

Slovic, P., and E. U. Weber. 2011. "Perception of Risk Posed by Extreme Events." In *Regulation of Toxic Substances and Hazardous Waste, 2nd Edition*, edited by J. S. Applegate, J. G. Laitos, J. M. Gaba, and N. M. Sachs. Foundation Press.

Smith, K. F., M. Goldberg, S. Rosenthal, L. Carlson, J. Chen, C. Chen, and S. Ramachandran. 2014. "Global Rise in Human Infectious Disease Outbreaks." *Journal of the Royal Society Interface* 11 (101): 20140950.

Sochas, L., A. A. Channon, and S. Nam. 2017. "Counting Indirect Crisis-Related Deaths in the Context of a Low-Resilience Health System: The Case of Maternal and Neonatal Cealth during the Ebola Epidemic in Sierra Leone." *Health Policy and Planning* 32 (suppl_3): iii32–iii39.

Stephens, P. R., M. Sundaram, S. Ferreira, N. Gottdenker, K. F. Nipa, A. M. Schatz, J. P. Schmidt, and J. M. Drake. 2022. "Drivers of African Filovirus (Ebola and Marburg) Outbreaks." *Vector-Borne and Zoonotic Diseases* 22 (9): 478–90.

Strouth, A., S. McDougall, M. Jakob, K. Holm, and E. Moase. 2019. "Quantitative Risk Management Process for Debris Flows and Debris Floods: Lessons Learned in Western Canada." 7th International Conference on Debris-Flow Hazards Mitigation. https://repository.mines.edu/server/api/core/bitstreams/f82115dc-54af-4296-86dd-6d869961987d/content.

Taubenberger, J. K., and D. M. Morens. 2006. "1918 Influenza: The Mother of All Pandemics." *Emerging Infectious Diseases* 12 (1): 15–22.

Troeger, C., B. Blacker, I. A. Khalil, P. C. Rao, J. Cao, S. R. Zimsen, S. B. Albertson, et al. 2018. "Estimates of the Global, Regional, and National Morbidity, Mortality, and Aetiologies of Lower Respiratory Infections in 195 Countries, 1990–2016: A Systematic Analysis for the Global Burden of Disease Study 2016." *The Lancet Infectious Diseases* 18 (11): 1191–210.

UN DESA (United Nations Department of Economic and Social Affairs). 2022. "World Population Prospects 2022: Data Sources." UN DESA/POP/2022/DC/NO. 9, United Nations, New York. https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/undesa_pd_2022_wpp-data_sources.pdf.

US Department of Health and Human Services. 2005. "HHS Pandemic Influenza Plan." US Department of Health and Human Services, Washington, DC. https://www.cdc.gov/pandemic-flu/media/hhspandemicinfluenzaplan.pdf.

van Wijhe, M., M. M. Ingholt, V. Andreasen, and L. Simonsen. 2018. "Loose Ends in the Epidemiology of the 1918 Pandemic: Explaining the Extreme Mortality Risk in Young Adults." *American Journal of Epidemiology* 187 (12): 2503–10.

Vinck, P., P. N. Pham, K. K. Bindu, J. Bedford, and E. J. Nilles. 2019. "Institutional Trust and Misinformation in the Response to the 2018–19 Ebola Outbreak in North Kivu, DR Congo: A Population-Based Survey." *The Lancet Infectious Diseases* 19 (5): 529–36.

Wacharapluesadee, S., S. Iamsirithawon, W. Chaifoo, T. Ponpinit, C. Ruchisrisarod, C. Sonpee, P. Katasrila, et al. 2020. "Identification of a Novel Pathogen Using Family-Wide PCR: Initial Confirmation of COVID-19 in Thailand." *Frontiers in Public Health* 8: 598.

Wegrzyn, R. D., G. D. Appiah, R. Morfino, S. R. Milford, A. T. Walker, E. T. Ernst, W. W. Darrow, et al. 2022. "Early Detection of SARS-CoV-2 Variants Using Traveler-Based Genomic Surveillance at Four US Airports, September 2021–January 2022." *MedRxiv* 2022.03. 21.22272490.

WHO (World Health Organization). 2020. "COVID-19 Emergency Committee Highlights Need for Response Efforts over Long Term." News release, August 1, 2020. https://www.who.int/news/item/01-08-2020-covid-19-emergency-committee-highlights-need-for-response-efforts-over-long-term.

WHO (World Health Organization). 2022. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int.

Wilkinson, C. 2021. "Pandemic Data Drives Risk Modeling." *Business Insurance*, February 2, 2021. https://www.businessinsurance.com/pandemic-data-drives-risk-modeling-covid-19-coronavirus/.

Wise, P. H., and M. Barry. 2017. "Civil War & the Global Threat of Pandemics." *Daedalus* 146 (4): 71–84.