Chapter 17

Pandemics: Risks, Impacts, and Mitigation

Nita Madhav, Ben Oppenheim, Mark Gallivan,
Prime Mulembakani, Edward Rubin, and Nathan Wolfe

INTRODUCTION

Pandemics are large-scale outbreaks of infectious disease that can greatly increase morbidity and mortality over a wide geographic area and cause significant economic, social, and political disruption. Evidence suggests that the likelihood of pandemics has increased over the past century because of increased global travel and integration, urbanization, changes in land use, and greater exploitation of the natural environment (Jones and others 2008; Morse 1995). These trends likely will continue and will intensify. Significant policy attention has focused on the need to identify and limit emerging outbreaks that might lead to pandemics and to expand and sustain investment to build preparedness and health capacity (Smolinsky, Hamburg, and Lederberg 2003).

The international community has made progress toward preparing for and mitigating the impacts of pandemics. The 2003 severe acute respiratory syndrome (SARS) pandemic and growing concerns about the threat posed by avian influenza led many countries to devise pandemic plans (U.S. Department of Health and Human Services 2005). Delayed reporting of early SARS cases also led the World Health Assembly to update the International Health Regulations (IHR) to compel all World Health Organization member states to meet specific standards for detecting, reporting on, and responding to outbreaks (WHO 2005). The framework put into place by the updated IHR contributed to a more coordinated global response during the 2009 influenza pandemic (Katz 2009). International donors also have begun to invest in improving preparedness through refined standards and funding for building health capacity (Wolicki and others 2016).

Despite these improvements, significant gaps and challenges exist in global pandemic preparedness. Progress toward meeting the IHR has been uneven, and many countries have been unable to meet basic requirements for compliance (Fischer and Katz 2013; WHO 2014). Multiple outbreaks, notably the 2014 West Africa Ebola epidemic, have exposed gaps related to the timely detection of disease, availability of basic care, tracing of contacts, quarantine and isolation procedures, and preparedness outside the health sector, including global coordination and response mobilization (Moon and others 2015; Pathmanathan and others 2014). These gaps are especially evident in resource-limited settings and have posed challenges during relatively localized epidemics, with dire implications for what may happen during a full-fledged global pandemic.

For the purposes of this chapter, an *epidemic* is defined as "the occurrence in a community or region of cases of an illness . . . clearly in excess of normal expectancy" (Porta 2014). A *pandemic* is defined as "an epidemic occurring over a very wide area, crossing international boundaries, and usually affecting a large number of people" (Porta 2014). Pandemics are, therefore, identified by their geographic scale rather than the severity of illness. For example, in contrast to annual seasonal influenza epidemics, *pandemic influenza* is

Corresponding Author: Nita Madhav, MSPH, Metabiota, San Francisco, California, United States; nmadhav@metabiota.com.

defined as "when a new influenza virus emerges and spreads around the world, and most people do not have immunity" (WHO 2010).

This chapter does not consider endemic diseases—those that are constantly present in particular localities or regions. Endemic diseases are far more common than pandemics and can have significant negative health and economic impacts, especially in low- and middle-income countries (LMICs) with weak health systems. Additionally, given the lack of historical data and extreme uncertainty regarding bioterrorism, this chapter does not specifically consider bioterrorism-related events, although bioterrorism could hypothetically lead to a pandemic.

This chapter covers the following findings concerning the risks, impacts, and mitigation of pandemics as well as knowledge gaps:

Risks

- Pandemics have occurred throughout history and appear to be increasing in frequency, particularly because of the increasing emergence of viral disease from animals.
- Pandemic risk is driven by the combined effects of spark risk (*where* a pandemic is likely to arise) and spread risk (*how likely* it is to diffuse broadly through human populations).
- Some geographic regions with high spark risk, including Central and West Africa, lag behind the rest of the globe in pandemic preparedness.
- Probabilistic modeling and analytical tools such as exceedance probability (EP) curves are valuable for assessing pandemic risk and estimating the potential burden of pandemics.
- Influenza is the most likely pathogen to cause a severe pandemic. EP analysis indicates that in any given year, a 1 percent probability exists of an influenza pandemic that causes nearly 6 million pneumonia and influenza deaths or more globally.

Impacts

- Pandemics can cause significant, widespread increases in morbidity and mortality and have disproportionately higher mortality impacts on LMICs.
- Pandemics can cause economic damage through multiple channels, including short-term fiscal shocks and longer-term negative shocks to economic growth.
- Individual behavioral changes, such as fear-induced aversion to workplaces and other public gathering places, are a primary cause of negative shocks to economic growth during pandemics.
- Some pandemic mitigation measures can cause significant social and economic disruption.
- In countries with weak institutions and legacies of political instability, pandemics can increase political stresses and tensions. In these contexts, outbreak response measures such as quarantines have sparked violence and tension between states and citizens.

Mitigation

- Pathogens with pandemic potential vary widely in the resources, capacities, and strategies required for mitigation. However, there are also common prerequisites for effective preparedness and response.
- The most cost-effective strategies for increasing pandemic preparedness, especially in resource-constrained settings, consist of investing to strengthen core public health infrastructure, including water and sanitation systems; increasing situational awareness; and rapidly extinguishing sparks that could lead to pandemics.
- Once a pandemic has started, a coordinated response should be implemented focusing on maintenance of situational awareness, public health messaging, reduction of transmission, and care for and treatment of the ill.
- Successful contingency planning and response require surge capacity—the ability to scale up the delivery of health interventions proportionately for the severity of the event, the pathogen, and the population at risk.
- For many poorly prepared countries, surge capacity likely will be delivered by foreign aid providers. This is a tenable strategy during localized outbreaks, but global surge capacity has limits that likely will be reached during a full-scale global pandemic as higher-capacity states focus on their own populations.
- Risk transfer mechanisms, such as risk pooling and sovereign-level catastrophe insurance, provide a viable option for managing pandemic risk.

Knowledge Gaps

- Spending and costs specifically associated with pandemic preparedness and response efforts are poorly tracked.
- There is no widely accepted, consistent methodology for estimating the economic impacts of pandemics.
- Most data regarding the impacts of pandemics and the benefits and costs of mitigation measures come from high-income countries (HICs), leading to biases and potential blind spots regarding the risks, consequences, and optimal interventions specific to LMICs.

PANDEMIC RISKS AND CONSEQUENCES

Importance of Pandemics

Pandemics can cause sudden, widespread morbidity and mortality as well as social, political, and economic disruption. The world has endured several notable pandemics, including the Black Death, Spanish flu, and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) (table 17.1).

Because the definition of pandemic primarily is geographic, it groups together multiple, distinct types of events and public health threats, all of which have their own severity, frequency, and other disease characteristics. Each type of event requires its own optimal preparedness and response strategy; however this chapter also discusses common prerequisites for effective response. The variety of pandemic threats is driven by the great diversity of pathogens and their interaction with humans. Pathogens vary across multiple dimensions, including the mechanism and dynamics of disease transmission, severity, and differentiability of associated morbidities. These and other factors determine whether cases will be identified and contained rapidly or whether an outbreak will spread (Fraser and others 2004). As a result, pathogens with pandemic potential also vary widely in the scale of their potential health, economic, and sociopolitical impacts as well as the resources, capacities, and strategies required for mitigation.

One must distinguish between several broad categories of pandemic threats. At one extreme are pathogens that have high potential to cause truly global, severe pandemics. This group includes pandemic influenza viruses. These pathogens transmit efficiently between humans, have sufficiently long asymptomatic infectious periods to facilitate the undetected movement of infected persons, and have symptomatic profiles that present challenges for differential diagnosis (particularly in the early periods of infection). A second group of pathogens presents a moderate global threat. These agents (for example, Nipah virus and H5N1 and H7N9 influenzas) have not demonstrated sustained human-to-human transmission but could become transmitted more efficiently as a result of mutations and adaptation. A third group of pathogens (for example, Ebola, Marburg, Lassa) has the potential to cause regional or interregional epidemics, but the risk of a truly global pandemic is limited because of the slow pace of transmission or high probability of detection and containment.

Among all known pandemic pathogens, influenza poses the principal threat because of its potential severity and semiregular occurrence since at least the 16th century (Morens and others 2010). The infamous 1918 influenza pandemic killed an estimated 20 million

Table 17.1 Notable Epidemics and Pandemics since the Middle Ages

Starting year	Event	Geographic extent	Estimated direct morbidity or mortality	Estimated economic, social, or political impact
1347	Bubonic plague (Black Death) pandemic	Eurasia	30–50 percent mortality of the European population (DeWitte 2014)	Likely hastened end of the feudal system in Europe (Platt 2014)
Early 1500s	Introduction of smallpox	Americas	More than 50 percent mortality in some communities (Jones 2006)	Destroyed native societies, facilitating the hegemony of European countries (Diamond 2009)
1881	Fifth cholera pandemic	Global	More than 1.5 million deaths (9.7 per 10,000 persons) (Chisholm 1911)	Sparked attacks on Russian tsarist government and medical officials (Frieden 1977)
1918	Spanish flu influenza pandemic	Global	20 million–100 million deaths (111–555 deaths per 10,000 persons) (Johnson and Mueller 2002)	GDP loss of 3 percent in Australia, 15 percent in Canada, 17 percent in the United Kingdom, 11 percent in the United States (McKibbin and Sidorenko 2006)
1957	Asian flu influenza pandemic	Global	0.7 million–1.5 million deaths (2.4–5.1 deaths per 10,000 persons) (Viboud and others 2016)	GDP loss of 3 percent in Canada, Japan, the United Kingdom, and the United States (McKibbin and Sidorenko 2006)
1968	Hong Kong flu influenza pandemic	Global	1 million deaths (2.8 deaths per 10,000 persons) (Mathews and others 2009)	US$23 billion–US$26 billion direct and indirect costs in the United States (Kavet 1977)

table continues next page

Table 17.1 Notable Epidemics and Pandemics since the Middle Ages (continued)

Starting year	Event	Geographic extent	Estimated direct morbidity or mortality	Estimated economic, social, or political impact
1981	HIV/AIDS pandemic	Global	More than 70 million infections, 36.7 million deaths (WHO Global Health Observatory data, http://www.who.int/gho/hiv/en/)	2–4 percent annual loss of GDP growth in Africa (Dixon, McDonald, and Roberts 2001)[a]
2003	SARS pandemic	4 continents, 37 countries	8,098 possible cases, 744 deaths (Wang and Jolly 2004)	GDP loss of US$4 billion in Hong Kong SAR, China; US$3 billion–US$6 billion in Canada; and US$5 billion in Singapore (Keogh-Brown and Smith 2008)
2009	Swine flu influenza pandemic	Global	151,700–575,500 deaths (0.2–0.8 per 10,000 persons) (Dawood and others 2012)	GDP loss of US$1 billion in the Republic of Korea (Kim, Yoon, and Oh 2013)
2012	MERS epidemic	22 countries	1,879 symptomatic cases, 659 deaths (Arabi and others 2017)	US$2 billion loss in the Republic of Korea, triggering US$14 billion in government stimulus spending (Jun 2015; Park and Kim 2015)
2013[b]	West Africa Ebola virus disease epidemic	10 countries	28,646 cases, 11,323 deaths (WHO 2016a)	US$2 billion loss in Guinea, Liberia, and Sierra Leone (World Bank 2014)
2015	Zika virus pandemic	76 countries	2,656 reported cases of microcephaly or central nervous system malformation (WHO 2017)	US$7 billion–US$18 billion loss in Latin America and the Caribbean (UNDP 2017)

Note: List of events is illustrative rather than exhaustive. All U.S. dollar amounts are rounded to nearest billion. GDP = gross domestic product; HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome; MERS = Middle East respiratory syndrome; SARS = severe acute respiratory syndrome.

a. Studies of the effects of HIV/AIDS on per capita gross national product have found smaller effects.

b. The West Africa Ebola virus outbreak occurred from 2013 to 2016, but the peak and international response efforts began in 2014.

to 100 million persons globally, with few countries spared (Johnson and Mueller 2002). Its severity reflects in part the limited health technologies of the period, when no antibiotics, antivirals, or vaccines were available to reduce transmission or mortality (Murray and others 2006).

During the 1918 pandemic, populations experienced significantly higher mortality rates in LMICs than in HICs, likely as a result of higher levels of malnutrition and comorbid conditions, insufficient access to supportive medical care, and higher rates of disease transmission (Brundage and Shanks 2008; Murray and others 2006). The mortality disparity between HICs and LMICs likely would be even greater today for a similarly severe event, because LMICs have disproportionately lower medical capacity, less access to modern medical interventions, and higher interconnectivity between population centers.

Origin of Pandemics

Most new pandemics have originated through the "zoonotic" transmission of pathogens from animals to humans (Murphy 1998; Woolhouse and Gowtage-Sequeria 2005), and the next pandemic is likely to be a zoonosis as well. Zoonoses enter into human populations from both domesticated animals (such as farmed swine or poultry) and wildlife. Many historically significant zoonoses were introduced through increased human-animal interaction following domestication, and potentially high-risk zoonoses (including avian influenzas) continue to emerge from livestock production systems (Van Boeckel and others 2012; Wolfe, Dunavan, and Diamond 2007). Some pathogens (including Ebola) have emerged from wildlife reservoirs and entered into human populations through the hunting and consumption of wild species (such as bushmeat), the wild animal trade, and other contact with wildlife (Pike and others 2010; Wolfe, Dunavan, and Diamond 2007).

Zoonotic pathogens vary in the extent to which they can survive within and spread between human hosts. As shown in table 17.2, the degree of zoonotic adaptation spans a continuum from transmission only within animal populations (stage 1) to transmission only within human populations (stage 5). Most zoonotic pathogens are not well adapted to humans (stages 2–3), emerge sporadically through spillover events, and may lead to localized outbreaks, called stuttering chains (Pike and others 2010; Wolfe and others 2005). These episodes of “viral chatter” increase pandemic risk by providing opportunities for viruses to become better adapted to spreading within a human population. Pathogens that are past stage 3 are of the greatest concern, because they are sufficiently adapted to humans to cause long transmission chains between humans (directly or indirectly through vectors), and their geographic spread is not constrained by the habitat range of an animal reservoir.

Pandemic Risk Factors

Pandemic risk, as noted, is driven by the combined effects of spark risk and spread risk. The foci of both risk factors often overlap, especially in some LMICs (such as in Central and West Africa and Southeast Asia), making these areas particularly vulnerable to pandemics and their negative consequences.

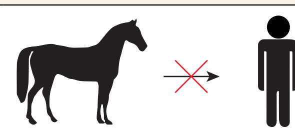
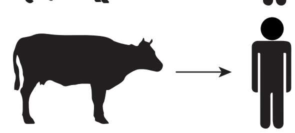
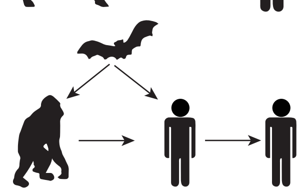
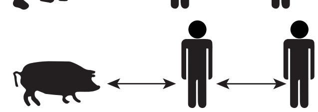
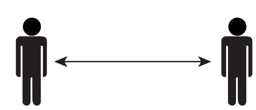
Spark Risk

A zoonotic spark could arise from the introduction of a pathogen from either domesticated animals or wildlife. Zoonoses from domesticated animals are concentrated in areas with dense livestock production systems, including areas of China, India, Japan, the United States, and Western Europe. Key drivers for spark risk from domesticated animals include intensive and extensive farming and livestock production systems and live animal markets, as well as the potential for contact between livestock and wildlife reservoirs (Gilbert and others 2014; Jones and others 2008). Wildlife zoonosis risk is distributed far more broadly, with foci in China, India, West and Central Africa, and the Amazon Basin (Jones and others 2008). Risk drivers include behavioral factors (such as bushmeat hunting and use of animal-based traditional medicines), natural resource extraction (such as sylviculture and logging), the extension of roads into wildlife habitats, and environmental factors (including the degree and distribution of animal diversity) (Wolfe and others 2005).

Spread Risk

After a spark or importation, the risk that a pathogen will spread within a population is influenced by pathogen-specific factors (including genetic adaptation and mode of transmission) and human population-level factors (such as the density of the population and the susceptibility to infection; patterns of movement driven by travel, trade, and migration; and speed and effectiveness of public health surveillance and response measures) (Sands and others 2016).

Table 17.2 Pathogen Adaptation and Pandemic Risk

Stage	Transmission to humans[a]	Pathogen example	Simplified transmission diagram
Stage 1: animal reservoir transmission only	None	H3N8 equine influenza virus	
Stage 2: primary infection	Only from animals	Anthrax	
Stage 3: limited outbreaks	Few human-to-human transmission chains	Marburg virus	
Stage 4: sustained outbreaks	Many human-to-human transmission chains	Pandemic A (H1N1) 2009 influenza virus	
Stage 5: predominant human transmission	Human-to-human	Smallpox virus	

Source: Adapted from Wolfe, Dunavan, and Diamond 2007.
a. Direct or indirect transmission through vector.

Dense concentrations of population, especially in urban centers harboring overcrowded informal settlements, can act as foci for disease transmission and accelerate the spread of pathogens (Neiderud 2015). Moreover, social inequality, poverty, and their environmental correlates can increase individual susceptibility to infection significantly (Farmer 1996). Comorbidities, malnutrition, and caloric deficits weaken an individual's immune system, while environmental factors such as lack of clean water and adequate sanitation amplify transmission rates and increase morbidity and mortality (Toole and Waldman 1990). Collectively, all these factors suggest that marginalized populations, including refugees and people living in urban slums and informal settlements, likely face elevated risks of morbidity and mortality during a pandemic.

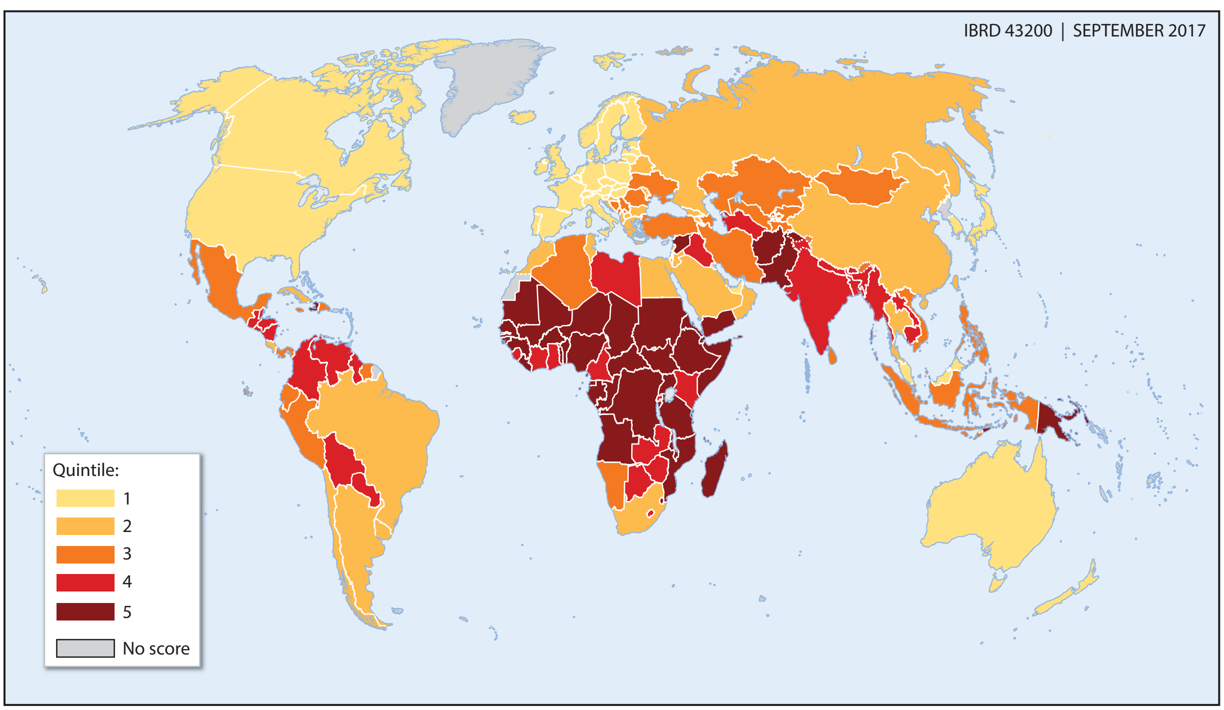
A country's expected ability to curtail pandemic spread can be expressed using a preparedness index developed by Oppenheim and others (2017). The index illustrates global variation in institutional readiness to detect and respond to a large-scale outbreak of infectious disease. It draws on the IHR core capacity metrics and other publicly accessible cross-national indicators. However, it diverges from the IHR metrics in its breadth and focus on measuring underlying and enabling institutional, infrastructural, and financial capacities such as the following (Oppenheim and others 2017):

- Public health infrastructure capable of identifying, tracing, managing, and treating cases
- Adequate physical and communications infrastructure to channel information and resources
- Fundamental bureaucratic and public management capacities
- Capacity to mobilize financial resources to pay for disease response and weather the economic shock of the outbreak
- Ability to undertake effective risk communications.

Well-prepared countries have effective public institutions, strong economies, and adequate investment in the health sector. They have built specific competencies critical to detecting and managing disease outbreaks, including surveillance, mass vaccination, and risk communications. Poorly prepared countries may suffer from political instability, weak public administration, inadequate resources for public health, and gaps in fundamental outbreak detection and response systems.

Map 17.1 presents the global distribution of epidemic preparedness, with countries grouped into quintiles. A geographic analysis of preparedness shows that some areas of high spark risk also are the least prepared. Geographic areas with high spark risk from domesticated animals (including China, North America, and Western Europe) have relatively higher levels of preparedness,

Map 17.1 Global Distribution of Epidemic Preparedness, 2017



Note: Countries are grouped into quintiles of epidemic preparedness (1 = most prepared, 5 = least prepared).

although China lags behind its counterparts. However, geographic areas with high spark risk from wildlife species (including Central and West Africa) have some of the lowest preparedness scores globally, indicating a potentially dangerous overlap of spark risk and spread risk.

Table 17.3 presents the average epidemic preparedness quintile across each of the World Bank's country income groups. National income alone offers an incomplete and potentially misleading metric of preparedness. Although income is correlated with epidemic preparedness, many countries are substantially better or worse prepared than expected, given their gross national income per capita.

Burden of Pandemics

Quantifying the morbidity and mortality burden from pandemics poses a significant challenge. Although estimates are available from historical events (table 17.1), the historical record is sparse and incomplete. To overcome these gaps in estimating the frequency and severity of pandemics, probabilistic modeling techniques can augment the historical record with a large catalog of hypothetical, scientifically plausible, simulated pandemics that represent a wide range of possible scenarios. Modeling can also better account for changes that have occurred since historical times, such as medical advances, changing demographics, and shifting travel patterns.

Scenario modeling of epidemics and pandemics can be achieved through large-scale computer simulations of global spread, dynamics, and illness outcomes of disease (Colizza and others 2007; Tizzoni and others 2012). These models allow for specification of parameters that may drive the likelihood of a spark (for example, location and frequency) and determinants of severity (for example, transmissibility and virulence). The models then simulate at a daily time step the spread of disease from person to person via disease transmission dynamics and from place to place via incorporation of long-range and short-range population movements. The models also can incorporate mitigation measures, seasonality, stochastic processes, and other factors that can vary during an epidemic. Millions of these simulations can be run with wide variation in the initial conditions and final outcomes.

These millions of simulations can be used to quantify the burden of pandemics through a class of probabilistic modeling called catastrophe modeling, which the insurance industry uses to understand risks posed by infrequent natural disasters such as hurricanes and earthquakes (Fullam and Madhav 2015; Kozlowski and Mathewson 1997). When applied to pandemics, this approach requires statistically fitting distributions of the parameters. These parameter distributions provide weightings of the likelihood of the different events. Through correlated statistical sampling based on the parameter weights, scenarios are selected for inclusion in an event catalog of simulated pandemic events. A schematic diagram shows how the catastrophe modeling process is used to develop the event catalog (figure 17.1).

Analysis of the event catalog yields annual EP curves (for example, as shown in figure 17.2), which provide a metric of the likelihood that an event of a given severity, or worse, begins in any given year. The EP curve is a visualization of the event catalog, in which the number of estimated deaths for each event is ranked in descending order. Because the event catalog includes scenarios incorporating spark probabilities and estimates of disease propagation, the EP curve includes the combined impacts of both spark risk and spread risk. Although a global curve is shown in figure 17.2, EP curves can be estimated for other geographic resolutions, such as a country or province.

Table 17.3 Epidemic Preparedness Score, by Country Income Group, 2017

Country income group[a]	Mean epidemic preparedness quintile[b]	Top-performing country in group	Bottom-performing country in group
High-income	1.3	Norway	Trinidad and Tobago
Upper-middle-income	2.9	Malaysia	Equatorial Guinea
Lower-middle-income	3.7	Armenia	Mauritania
Low-income	4.8	Nepal	Somalia

Source: The epidemic preparedness index draws on indicators from the World Health Organization, World Bank, United Nations agencies, and nongovernmental sources (see Oppenheim and others 2017).

a. Income groups follow World Bank income classifications for fiscal 2018, based on estimates of 2016 gross national income per capita and calculated using the World Bank Atlas method: high-income (US$12,236 or more), upper-middle-income (US$3,956–US$12,235), lower-middle-income (US$1,006–US$3,955), and low-income (US$1,005 or less). For further explanation, see https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.

b. Countries are grouped into quintiles of epidemic preparedness (1 = most prepared, 5 = least prepared).

Figure 17.1 Process for Generating the Event Catalog

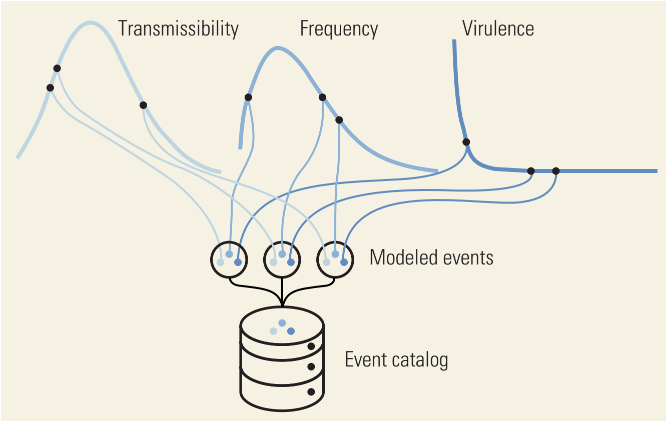
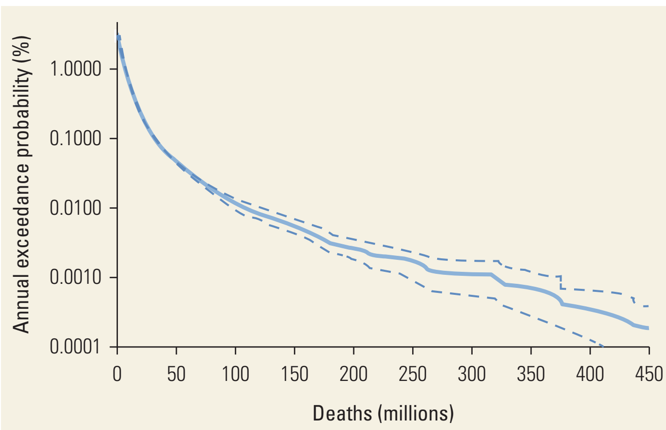


Figure 17.2 Estimated Annual Exceedance Probability Curve for Global Pneumonia and Influenza Deaths Caused by Influenza Pandemics, 2017



Source: Metabiota simulations.
Note: Annual exceedance probability is the likelihood that an event of a given severity, or worse, begins in any given year. Dashed lines indicate the 5th and 95th percentile bands.

The EP curve is a powerful tool that yields several key findings regarding the frequency and severity of potential pandemics. Applied to influenza pandemics, we find the following:

- An influenza pandemic having the global mortality rate observed during the 2009 Swine flu pandemic (0.2–0.8 deaths per 10,000 persons) or worse has about a 3 percent probability of occurring in any given year.
- In any given year, the probability of an influenza pandemic causing nearly 6 million pneumonia and influenza deaths (8 deaths per 10,000 persons) or more globally is 1 percent.
- The annual probability of an influenza pandemic's meeting or exceeding the global mortality rate of the 1918 Spanish flu pandemic (111–555 deaths per 10,000 persons) is less than 0.02 percent.
- As indicated by the heavy tail of the EP curve, most of the potential burden from influenza pandemics comes from the most severe pandemics.

Table 17.4 shows select EPs for influenza pandemics in low-, middle-, and high-income countries, based on further analysis of the event catalog. For example, in any given year, all LICs combined have a 3 percent probability of experiencing at least 140,000 deaths attributable to an influenza pandemic and a 0.1 percent chance of experiencing at least 8.3 million deaths. LICs bear a substantial burden of mortality risk from influenza pandemics. Strikingly, LICs contain only about 9 percent of the global population, yet they would contribute nearly 25 percent of deaths during an influenza pandemic.

Based on the event catalog, the average estimated global mortality from pneumonia and influenza during

Table 17.4 Select Annual Exceedance Probabilities for Pneumonia and Influenza Deaths Caused by Influenza Pandemics, by Country Income Level, 2017

Annual exceedance probability (%)	Deaths (millions)			
	Low income	Middle income	High income	Total
3.0	0.1	0.4	0.05	0.6
2.0	0.6	1.5	0.1	2.2
1.0	1.5	4.0	0.4	5.9
0.5	2.7	7.6	0.9	11.2
0.2	5.5	14.8	1.7	22.0
0.1	8.3	22.5	2.5	33.3

Source: Metabiota simulations.
Note: Annual exceedance probability is the likelihood that an event of a given severity, or worse, begins in any given year. Rows may not sum to total value due to rounding.

an influenza pandemic is more than 7.3 million deaths. However, because influenza pandemics occur on average once every 25–30 years, the average annual pneumonia and influenza mortality from influenza pandemics is a little more than 230,000 deaths. This is comparable to seasonal influenza, which worldwide causes at least 250,000 deaths annually (WHO 2016b). Although both numbers reflect an annual average, they differ in the combination of frequency and severity. Seasonal influenza deaths occur every year, but pandemic influenza deaths occur much less frequently, are concentrated in larger spikes, and affect a younger demographic.

When pandemics cause large morbidity and mortality spikes, they are much more likely to overwhelm health systems. Overwhelmed health systems and other indirect effects may contribute to a 2.3-fold increase in all-cause mortality during pandemics, although attribution of the causative agent is difficult (Simonsen and others 2013). If indirect deaths are taken into account, the average annual global deaths from influenza pandemics could be greater than 520,000, although there is a significant uncertainty in the estimate.

Pandemics caused by pathogens other than influenza also must be considered. Novel coronaviruses (such as SARS-CoV), filoviruses (such as Ebola virus), and flaviviruses (such as Zika virus) have caused large epidemics and pandemics. These viruses, like influenza, are ribonucleic acid viruses that have high mutation rates. Noninfluenza viruses typically cause more frequent, smaller epidemics but also an overall lower burden of morbidity and mortality than pandemic influenza. For diseases caused by coronaviruses and filoviruses, the lower burden stems from the mode of transmission, which often requires closer and more sustained contact than influenza does to spread.

Consequences of Pandemics

Health Impacts

The direct health impacts of pandemics can be catastrophic. During the Black Death, an estimated 30–50 percent of the European population perished (DeWitte 2014). More recently, the HIV/AIDS pandemic has killed more than 35 million persons since 1981 (WHO Global Health Observatory data, http://www.who.int/gho/hiv/en).

Pandemics can disproportionately affect younger, more economically active segments of the population (Charu and others 2011). During influenza pandemics (as opposed to seasonal outbreaks of influenza), the morbidity and mortality age distributions shift to younger populations, because younger people have lower immunity than older people, which significantly increases the years of life lost (Viboud and others 2010). Furthermore, many infectious diseases can have chronic effects, which can become more common or widespread in the case of a pandemic. For example, Zika-associated microcephaly has lifelong impacts on health and well-being.

The indirect health impacts of pandemics can increase morbidity and mortality further. Drivers of indirect health impacts include diversion or depletion of resources to provide routine care and decreased access to routine care resulting from an inability to travel, fear, or other factors. Additionally, fear can lead to an upsurge of the "worried well" seeking unnecessary care, further burdening the health care system (Falcone and Detty 2015).

During the 2014 West Africa Ebola epidemic, lack of routine care for malaria, HIV/AIDS, and tuberculosis led to an estimated 10,600 additional deaths in Guinea, Liberia, and Sierra Leone (Parpia and others 2016). This indirect death toll nearly equaled the 11,300 deaths directly caused by Ebola in those countries (WHO 2016a). Additionally, diversion of funds, medical resources, and personnel led to a 30 percent decrease in routine childhood immunization rates in affected countries (UNDP 2014). During the 2009 influenza pandemic, a greater surge in hospital admissions for influenza and pneumonia was associated with statistically significant increases in deaths attributable to acute myocardial infarction and stroke (Rubinson and others 2013). However, during a pandemic, distinguishing which deaths are attributable to the pandemic itself and which are merely coincidental may be impossible.

During the 2014 West Africa Ebola epidemic, facilities closures as a result of understaffing and fear of contracting the disease played a large role in lack of access to or avoidance of routine health care. One study of 45 public facilities in Guinea found that the Ebola outbreak led to a 31 percent decrease in outpatient visits for routine maternal and child health services (Barden-O'Fallon and others 2015). Among children under age five years, hospitals witnessed a 60 percent decrease in visits for diarrhea and a 58 percent decrease in visits for acute respiratory illness (ARI), while health centers saw a 25 percent decrease in visits for diarrhea and a 23 percent decrease in visits for ARI. In Sierra Leone, visits to public facilities for reproductive health care fell by as much as 40 percent during the outbreak (UNDP 2014).

The availability of health care workers also decreases during a pandemic because of illness, deaths, and fear-driven absenteeism. Viral hemorrhagic fevers such as Ebola take an especially severe toll on health care workers, who face significant exposure to infectious material:

- *During the first Ebola outbreak* in the Democratic Republic of Congo in 1976 (then called Zaire), the Yambuku Mission Hospital—at the epicenter of the outbreak—was closed because 11 out of the 17 staff members had died of the disease (WHO 1978).
- *During the Kikwit Ebola outbreak in 1995* in the same country, 24 percent of cases occurred among known or possible health care workers (Rosello and others 2015).
- *During the 2014 West Africa Ebola epidemic*, health care workers experienced high mortality rates: 8 percent of doctors, nurses, and midwives succumbed to Ebola in Liberia, 7 percent in Sierra Leone, and 1 percent in Guinea (Evans, Goldstein, and Popova 2015).

Even if health care workers do not die, their ability to provide care may be reduced. At the peak of a severe influenza pandemic, up to 40 percent of health care workers might be unable to report for duty because they are ill themselves, need to care for ill family members, need to care for children because of school closures, or are afraid (Falcone and Detty 2015; U.S. Homeland Security Council 2006).

Economic Impacts

Pandemics can cause acute, short-term fiscal shocks as well as longer-term damage to economic growth. Early-phase public health efforts to contain or limit outbreaks (such as tracing contacts, implementing quarantines, and isolating infectious cases) entail significant human resource and staffing costs (Achonu, Laporte, and Gardam 2005). As an outbreak grows, new facilities may need to be constructed to manage additional infectious cases; this, along with increasing demand for consumables (medical supplies, personal protective equipment, and drugs) can greatly increase health system expenditures (Herstein and others 2016).

Diminished tax revenues may exacerbate fiscal stresses caused by increased expenditures, especially in LMICs, where tax systems are weaker and government fiscal constraints are more severe. This dynamic was visible during the 2014 West Africa Ebola epidemic in Liberia: while response costs surged, economic activity slowed, and quarantines and curfews reduced government capacity to collect revenue (World Bank 2014).

During a mild or moderate pandemic, unaffected HICs can offset fiscal shocks by providing increased official development assistance (ODA) to affected countries, including direct budgetary support. However, during a severe pandemic where HICs confront the same fiscal stresses and may be unable or unwilling to provide assistance, LMICs could face larger budget shortfalls, potentially leading to weakened public health response or cuts in other government spending.

The direct fiscal impacts of pandemics generally are small, however, relative to the indirect damage to economic activity and growth. Negative economic growth shocks are driven directly by labor force reductions caused by sickness and mortality and indirectly by fear-induced behavioral changes. Fear manifests itself through multiple behavioral changes. As an analysis of the economic impacts of the 2014 West Africa Ebola epidemic noted, "Fear of association with others . . . reduces labor force participation, closes places of employment, disrupts transportation, motivates some governments to close land borders and restrict entry of citizens from affected countries, and motivates private decision makers to disrupt trade, travel, and commerce by canceling scheduled commercial flights and reducing shipping and cargo services" (World Bank 2014). These effects reduce labor force participation over and above the pandemic's direct morbidity and mortality effects and constrict local and regional trade.

The indirect economic impact of pandemics has been quantified primarily through computable general equilibrium simulations; the empirical literature is less developed. World Bank economic simulations indicate that a severe pandemic could reduce world gross domestic product (GDP) by roughly 5 percent (Burns, Van der Mensbrugghe, and Timmer 2006). The reduction in demand caused by aversive behavior (such as the avoidance of travel, restaurants, and public spaces, as well as prophylactic workplace absenteeism) exceeds the economic impact of direct morbidity- and mortality-associated absenteeism.

These results align with country-specific estimates: an analysis of pandemic influenza's impact on the United Kingdom found that a low-severity pandemic could reduce GDP by up to 1 percent, whereas a high-severity event could reduce GDP by 3–4 percent (Smith and others 2009). The World Bank's estimates from the 2014 West Africa Ebola epidemic suggest that economic disruption in low-income countries (LICs) could be even greater. For example, the 2015 economic growth estimate for Liberia was 3 percent (against a pre-Ebola estimate of 6.8 percent); for Sierra Leone, it was −2 percent (against a pre-Ebola estimate of nearly 9 percent) (Thomas and others 2015).

Finally, estimates of fiscal and growth shocks are significant but do not include the intrinsic value of lives lost. Fan, Jamison, and Summers (2016) consider this additional dimension of economic loss by estimating the value of excess deaths across varying levels of modeled pandemic severity, finding that the bulk of the expected annual loss from pandemics is driven by the direct cost of mortality, particularly in the case of low-probability, severe events.

During a severe pandemic, all sectors of the economy—agriculture, manufacturing, services—face disruption, potentially leading to shortages, rapid price increases for staple goods, and economic stresses for households, private firms, and governments. A sustained, severe pandemic on the scale of the 1918 influenza pandemic could cause significant and lasting economic damage.

Social and Political Impacts

Evidence suggests that epidemics and pandemics can have significant social and political consequences, creating clashes between states and citizens, eroding state capacity, driving population displacement, and heightening social tension and discrimination (Price-Smith 2009).

Severe premodern pandemics have been associated with significant social and political upheaval, driven by large mortality shocks and the resulting demographic shifts. Most notably, deaths arising from the introduction of smallpox and other diseases to the Americas led directly to the collapse of many indigenous societies and weakened the indigenous peoples' institutions and military capacity to the extent that they became vulnerable to European conquest (Diamond 2009; see table 17.1). Subsequent pandemics have not had such dramatic effects on political and social stability, primarily because the potential mortality shock has been attenuated by improvements in prevention and care.

Evidence does suggest that epidemics and pandemics can amplify existing political tensions and spark unrest, particularly in fragile states with legacies of violence and weak institutions. During the 2014 West Africa Ebola epidemic, steps taken to mitigate disease transmission, such as the imposition of quarantines and curfews by security forces, were viewed with suspicion by segments of the public and opposition political leaders. This led directly to riots and violent clashes with security forces (McCoy 2014). Latent political tensions from previously warring factions in Liberia also reemerged early in the epidemic and were linked with threats to health care workers as well as attacks on public health personnel and facilities.

The Ebola epidemic also greatly amplified political tensions in Guinea, Liberia, and Sierra Leone, with incumbent politicians accused of leveraging the crisis and disease control measures to cement political control and opposition figures accused of hampering disease response efforts (ICG 2015). Whereas growing tensions did not lead to large-scale political violence or instability, they did complicate public health response efforts. In Sierra Leone, quarantine in opposition-dominated regions was delayed because of concerns that it would be seen as politically motivated (ICG 2015). In countries with high levels of political polarization, recent civil war, or weak institutions, sustained outbreaks could lead to more sustained and challenging political tensions.

Pandemics also can have longer-term impacts on state capacity (Price-Smith 2001). The HIV/AIDS pandemic offers one notable example. The 1990s and early 2000s saw extremely high HIV/AIDS prevalence rates among African militaries, leading to increased absenteeism, decreased military capacity, and decreased readiness (Elbe 2002). Similar effects may occur during shorter, more acute pandemics, reducing state capacity to manage instability. The weakening of security forces can, in turn, amplify the risk of civil war and other forms of violent conflict (Fearon and Laitin 2003).

Large-scale outbreaks of infectious disease have direct and consequential social impacts. For example, widespread public panic during disease outbreaks can lead to rapid population migration. A 1994 outbreak of plague in Surat, India, caused only a small number of reported cases, but fear led some 500,000 people (roughly 20 percent of the city's population, including a disproportionately large number of clinicians) to flee their homes (Barrett and Brown 2008). Sudden population movements can have destabilizing effects, and migrants face elevated health risks arising from poor sanitation, poor nutrition, and other stressors (Toole and Waldman 1990). Migration also poses the risk of further spreading an outbreak.

Finally, outbreaks of infectious disease can cause already vulnerable social groups, such as ethnic minority populations, to be stigmatized and blamed for the disease and its consequences (Person and others 2004). During the Black Death, Jewish communities in Europe faced discrimination, including expulsion and communal violence, because of stigma and blame for disease outbreaks (Cohn 2007). Modern outbreaks have seen more subtle forms of discrimination, such as shunning and fear, directed at minority populations linked with disease foci. For example, Africans in Hong Kong SAR, China, reported experiencing social isolation, anxiety, and economic hardship resulting from fears of their association with Ebola (Siu 2015).

Trends Affecting Pandemic Risk

In recent decades, several trends have affected pandemic probability, preparedness, and mitigation capacity. Various factors—population growth, increasing urbanization, greater demand for animal protein, greater travel and connectivity between population centers, habitat loss, climate change, and increased interactions at the human-animal interface—affect the likelihood of pandemic events by increasing either the probability of a spark event or the potential spread of a pathogen (Tilman and Clark 2014; Tyler 2016; Zell 2004). With global population estimated to reach 9.7 billion by 2050 and with travel and trade steadily intensifying, public health systems will have less time to detect and contain a pandemic before it spreads (Tyler 2016).

As for poverty, the trends are mixed. On the positive side, enormous gains in poverty reduction have decreased the number of people living in extreme poverty. This may attenuate the mortality shock of a mild pandemic somewhat. On the negative side, extreme poverty is now concentrated in a small number of low-growth, high-poverty countries (Chandy, Kato, and Kharas 2015). In such countries, progress in building health system capacity also has been far slower.

Likewise, for a subset of countries with endemically weak institutions, building institutional capacity for complex tasks like pandemic mitigation and response is likely to be a slow process even under the most optimistic assumptions (Pritchett, Woolcock, and Andrews 2013). Many of these countries are in areas with high spark risk, particularly in Central and West Africa, and thus may remain vulnerable and require significant international assistance during a pandemic.

Other environmental and population trends that could increase the severity of pandemics include the persistence of slums, unresponsive health systems, higher prevalence of comorbidities, weaker sanitation, and aging populations (Arimah 2010; UNDESA 2015). The increasing threat posed by antibiotic resistance also could amplify mortality during pandemics of bacterial diseases such as tuberculosis and cholera and even viral diseases (especially for influenza, in which a significant proportion of deaths is often the result of bacterial pneumonia coinfections) (Brundage and Shanks 2008; Van Boeckel and others 2014).

PANDEMIC MITIGATION: PREPAREDNESS AND RESPONSE

Pandemic preparedness and response interventions can be classified by their timing with respect to pandemic occurrence: the prepandemic period, the spark period, and the spread period, as shown in box 17.1.

Whereas some interventions clearly fall under the purview of a single authority, responsibility for implementing and scaling up many critical aspects of preparedness and response is spread across multiple authorities, which

Box 17.1

Examples of Pandemic Preparedness and Response Activities, by Time Period

Prepandemic period (before a pandemic starts)

- Stockpile building
- Continuity planning
- Public health workforce training
- Simulation exercises
- Risk transfer mechanism set-up
- Situational awareness[a]

Spark period (as a pandemic starts)

- Initial outbreak detection
- Pathogen characterization or laboratory confirmation
- Risk communication and community engagement
- Animal disease control
- Contact tracing, quarantine, and isolation
- Situational awareness[a]

Spread period (after a pandemic starts)

- Global pandemic declaration
- Risk communications
- Contact tracing, quarantine, and isolation
- Social distancing
- Stockpile deployment
- Vaccine or antiviral administration
- Care and treatment
- Situational awareness[a]

a. Situational awareness includes passive and active animal and human disease surveillance and monitoring of public health facilities and resources.

play complementary, interlocking, and, in some cases, overlapping roles (Brattberg and Rhinard 2011). The governance of pandemic preparedness and response is complex, with authority fragmented across international, national, and subnational institutions, as well as among multiple organizations with functional responsibility for specific tasks (Hooghe and Marks 2003). Pandemic preparedness requires close coordination across public and private sector actors: vaccine development requires close coordination between government and vaccine producers; whereas critical response measures—such as managing quarantines—requires engagement between nonprofit organizations (hospitals, clinics, and nongovernmental organizations), public health authorities, affected communities and civil society groups, and the security sector.

Historical pandemics offer only a partial view to guide preparedness and response activities. Many countries and organizations have used the historical influenza pandemics in 1918, 1957, and 1968 to estimate the potential morbidity and mortality burden during a future pandemic (WHO 2016c). However, using these moderate-to-severe events to plan for a mild pandemic (for example, the 2009 influenza pandemic) can lead to an overzealous response—such as widespread mandatory school closures—that may create unintended negative economic consequences (Kelly and others 2011). And although the 1918 influenza pandemic is sometimes considered a "worst-case scenario" for planning purposes, possible scenarios today could be far more damaging—such as if a highly transmissible, highly virulent influenza virus were to emerge. Especially in LMICs, intensive care unit (ICU) beds and therapies for acute respiratory distress syndrome are in short supply, which could lead to many casualties (Osterholm 2005).

Situational Awareness

Situational awareness—in the context of pandemic preparedness—can be defined as having an accurate, up-to-date view of potential or ongoing infectious disease threats (including through traditional surveillance in humans and animals) and the resources (human, financial, informational, and institutional) available to manage those threats (ASPR 2014). Situational awareness is a crucial activity at all stages of a pandemic, including prepandemic, spark, and spread periods. It requires the support of health care resources (such as hospitals, doctors, and nurses), diagnostic infrastructure, and communications systems. It also requires the population to have access to and trust in the health care system.

Situational awareness supports policy decisions by tracking if and where disease transmission is occurring, detecting the most effective methods to reduce transmissibility, and deciding where to allocate resources. During a pandemic, situational awareness allows for monitoring to understand the course a pandemic is taking and whether intervention measures are effective.

The ability to detect the presence of a pandemic requires the health care workforce to recognize the illness and to have the technical and laboratory capacity to identify the pathogen (or rule out known pathogens) and respond to surges of clinical specimens in a timely manner. Rapid identification reduces risk by enabling infected persons to be isolated and given appropriate clinical care. During the 2003 SARS pandemic, a one-week delay in applying control measures may have nearly tripled the size of the outbreak and increased its duration by four weeks (Wallinga and Teunis 2004).

Endemic infectious diseases can affect pandemic detection by complicating the differential diagnosis and rapid identification of pandemic cases. Overlapping symptoms between endemic and emerging pathogens—for instance, between dengue and Zika or between malaria and Ebola—have hampered the early identification of cases (de Wit and others 2016; Waggoner and Pinsky 2016). This difficulty suggests a role for investment in the development and deployment of rapid diagnostic tests in regions with a high burden of endemic pathogens and high risk of disease emergence or importation (Yamey and others 2017). Additional constraints affecting epidemic and pandemic situational awareness in LMICs are described in box 17.2.

Preventing and Extinguishing Pandemic Sparks

Although most pandemic preparedness activities focus on reducing morbidity and mortality after a pandemic has spread widely, certain activities may prevent and contain pandemic sparks before they become a wider threat. At the core of pandemic prevention is the concept of One Health, an approach that considers human health, animal health, and the environment to be fundamentally interconnected (Zinsstag and others 2005).[1] Activities that focus on understanding and controlling zoonotic pathogens may prevent spillover events and subsequent pandemics (Morse and others 2012).

To understand the etiology of pandemics, important One Health activities include the surveillance of zoonotic pathogens of pandemic potential at the human-animal interface, the modeling of evolutionary dynamics, the risk assessments of zoonotic pathogens, and other methods of understanding the interplay between environmental changes and pathogen emergence (Paez-Espino and others 2016; Wolfe and

Box 17.2

Situational Awareness Constraints in Low- and Middle-Income Countries

Perhaps the greatest challenge in epidemic and pandemic response is the timely identification and notification of the first pandemic case. However, low- and middle-income countries are substantially slower than high-income countries to identify and communicate infectious disease outbreaks (Chan and others 2010). In most outbreaks, the first (or index) case is found retrospectively. Reporting delays result from multiple factors, which are discussed here. Moreover, the epidemiological characteristics of the index case often are difficult to ascertain, particularly in settings with limited diagnostic and laboratory capacity.

Patients infected with potentially pandemic pathogens may present with nonspecific symptoms, making discriminating between endemic and novel or significant pathogens difficult unless differential diagnostic tools are available. Gaps in health system access and surveillance system coverage also hamper identification and reporting. In such cases, an incipient epidemic will be identified only after sufficient deaths have occurred to draw the attention of health authorities. Particularly in areas where health system gaps are significant, monitoring unofficial sources of information, including rumors, may be useful (Samaan and others 2005).

Even once a potentially unusual or significant case has been identified, delays can be caused by low statistical capacity, low data management capacity, and low communication capacity among local frontline health workers. Delays also can arise from how surveillance and reporting systems are designed—for example, if health workers routinely report potentially significant cases at the end of the month rather than when they are identified.

Another constraint arises from inconsistencies in real-time reporting of data. During an outbreak response, national and regional health authorities must have strong relationships with local health providers to understand how data are generated and reported at the clinical level. Robust monitoring and data validation procedures, such as the use of global positioning systems and case-based systems, along with positive incentives for correct reporting, may help to alleviate such problems (Mancini and others 2014).

others 2005). For example, the PREDICT project of the U.S. Agency for International Development (USAID) has invested a significant amount of resources in understanding and characterizing zoonotic risk (Anthony and others 2013).[2]

Countries can focus their spark mitigation efforts on policies designed to control animal reservoirs; monitor high-risk populations such as people working at the animal interface (for example, those involved in animal husbandry, animal slaughter, and so on); and maintain robust animal health infrastructure, biosecurity, and veterinary public health capacities (Jonas 2013; Pike and others 2010; Watts 2004; Yu and others 2014).

Risk Communications

Risk communications can play a significant role in the control of an emerging epidemic or pandemic by providing information that people can use to take protective and preventive action (WHO 2013c). The dissemination of basic information (such as how the pathogen is transmitted, guidance on managing patient care, high-risk practices, and protective behavioral measures) can rapidly and significantly reduce the transmission of disease.

The way in which risk communications are framed and transmitted matters a great deal; they must be clear, simple, timely, and delivered by credible messengers. Factors such as literacy rates, cultural sensitivities, familiarity with scientific principles (such as the germ theory of disease), and reliance on oral versus written traditions all have implications for how messages should be designed and delivered (Bedrosian and others 2016).

Public health officials also need to identify and address misinformation, rumors, and anxieties. This can be a significant challenge. During the 2014 West Africa Ebola epidemic, many communities reached for culturally familiar explanations of disease transmission and rejected disease control practices that clashed with their traditional healing and burial practices (Roca and others 2015). Still other individuals spread rumors about the source of the infection; for example, in Liberia some community leaders claimed that the disease was created by the government (Epstein 2014).

Rumors can impede disease control and can be amplified by mistrust of government officials, which is a significant challenge in LMICs with high levels of corruption or legacies of violent conflict and social division. Research has found that in unstable contexts, people tend to believe rumors that confirm their preexisting beliefs and anxieties (Greenhill and Oppenheim 2017). This finding suggests that countering rumors with facts alone will not be sufficient. Risk communications need to be both factual and empathetic, addressing unfolding events and underlying fears through the lens of community experiences, histories, and perceptions.

The effectiveness of risk communications is difficult to measure. However, previous risk communication efforts have brought forth overarching themes that may be beneficial during the next epidemic or pandemic. One notable model comes from a Nipah virus outbreak in Bangladesh in 2010. In that outbreak, investigators found that messages about the sources of infection and potential strategies to reduce risk were more effective when conveyed by trusted local leaders and in terms that were relevant and grounded in the shared experiences of the affected community (Parveen and others 2016).

Reducing Pandemic Spread

Once a pandemic has begun in earnest, public health efforts often focus on minimizing its spread. Limiting the spread of a pandemic can help to reduce the number of total people who are infected and thus also mitigate some of the indirect health and economic effects. Strategies to minimize pandemic spread include the following (Ferguson and others 2005):

- *Curtailing interactions* between infected and uninfected populations: for example, through patient isolation, quarantine, social distancing practices, and school closures
- *Reducing infectiousness* of symptomatic patients: for example, through antiviral and antibiotic treatment and infection control practices
- *Reducing susceptibility* of uninfected individuals: for example, through vaccines.

During the prepandemic period, plans for implementing those measures should be developed and tested through simulation exercises.

Curtailing Interactions between Infected and Uninfected Populations

The methods for curtailing interactions between infected and uninfected populations include patient isolation, quarantine, social distancing practices, school closures, use of personal protective equipment, and travel restrictions.

The practice of quarantine began in the fourteenth century in response to the Black Death and continues today (Mackowiak and Sehdev 2002). Quarantine and social distancing (such as the prohibition of mass gatherings) during the 1918 influenza pandemic reduced spread and mortality rates, particularly when implemented in the early stages of the pandemic (Bootsma and Ferguson 2007; Hollingsworth, Ferguson, and Anderson 2006). During SARS and Ebola outbreaks, health agencies and hospitals limited disease spread by isolating symptomatic patients, quarantining patient contacts, and improving hospital infection control practices (Cohen and others 2016; Twu and others 2003). During the 2003 SARS pandemic, none of the health care workers in hospitals in Hong Kong SAR, China, who reported appropriate and consistent use of masks, gloves, gowns, and hand washing (as recommended under droplet and contact precautions) were infected (Seto and others 2003).

Travel restrictions are sometimes implemented by governments to curtail disease spread. Fear and lack of scientific understanding may motivate the imposition of travel restrictions (Flahault and Valleron 1990). As such, these measures are sometimes implemented for inappropriate pathogens or too late to contain an outbreak and can cause substantial economic damage and public anxiety. Travel restrictions are more beneficial for pathogens that do not have a significant asymptomatic carrier state and have a relatively long incubation period (for example, SARS and Ebola). However, such restrictions may be of limited efficacy for influenza pandemics unless initiated when there are fewer than 50 cases at the spark site (Ferguson and others 2005).

Reducing Infectiousness and Susceptibility

Vaccines, antibiotics, and antiviral drugs can play a critical role in mitigating a pandemic by reducing the infectiousness of symptomatic patients and the susceptibility of uninfected individuals. Antivirals may reduce influenza transmission, although the extent of their effectiveness is unclear (Ferguson and others 2005; Jefferson and others 2014). A systematic review of clinical trial data among treated adults showed that oseltamivir reduced the duration of influenza symptoms by 17 hours, but prophylaxis trials found no significant reduction of transmission (Jefferson and others 2014).

If available, vaccines can reduce susceptibility. Significant efforts have focused on speeding up vaccine development and scaling up production. However, the availability of vaccines—particularly in LMICs—depends on the affected area's capacity for distribution (including the scale and integrity of the cold chain), its capacity for last-mile delivery to rural areas, and the population's willingness to adopt the vaccine. Vaccination strategies targeting younger populations may be especially beneficial, in part because influenza transmissibility is higher among younger populations during pandemics (Miller and others 2008).

The effectiveness of antivirals, antibiotics, and vaccines in reducing spread diminishes if the pandemic is already global, if LMICs cannot afford adequate vaccine stocks for their populations, or if specific populations (for example, the poor or the socially vulnerable) cannot access vaccines. Additionally, pandemics may be caused by a pathogen without an available vaccine or efficacious biomedical therapy. Efforts to improve the vaccine development pipeline are underway (box 17.3).

Care and Treatment to Reduce the Severity of Pandemic Illness

During a pandemic, health authorities work to reduce the severity of illness through patient care and treatment, which can help decrease the likelihood of severe outcomes such as hospitalizations and deaths. Treatments may range from nonspecific, supportive care to disease-specific drugs. During the prepandemic period, plans to implement these measures should be developed and tested through simulation exercises.

Maintaining supportive care during an epidemic or pandemic can improve mortality rates by alleviating the symptoms of disease. During the 2014 West Africa Ebola epidemic, for example, evidence suggests that earlier case identification, supportive care, and rehydration therapy modestly reduced mortality (Walker and Whitty 2015). Indeed, despite the unavailability of antivirals or vaccines, efforts to engage communities with added medical supplies and trained clinicians decreased the case-fatality ratio moderately as more patients trusted, sought, and received clinical care (Aylward and others 2014).

Box 17.3

Vaccine Research and Development to Meet Pandemic Threats

Current vaccine research, development, and production time lines are not conducive to quick responses to pandemic threats. For example, despite biomedical advances, most influenza vaccines are produced through vaccine platforms that rely on the availability of embryonated chicken eggs and can take several months to produce (Reperant, Rimmelzwaan, and Osterhaus 2014). Vaccines that are in development may take decades to become available for human use. For example, Ebola vaccines were in development for more than a decade, with the first vaccine approved for clinical use only in 2015 (Henao-Restrepo and others 2016; Richardson and others 2010).

Several areas of active research seek to hasten and strengthen vaccine development. Of note is the World Health Organization's Global Action Plan for Influenza Vaccines, whose mission, in part, is to increase the capacity to produce vaccines for global influenza pandemics, quicken the production of vaccines, and research a universal influenza vaccine (Nannei and others 2016). Egg-independent cell culture platforms also have become a reality: in 2013 the U.S. Food and Drug Administration approved an influenza vaccine produced in insect cell lines (Milián and Kamen 2015).

In preparation for a noninfluenza pandemic, the public-private Coalition for Epidemic Preparedness Innovations (CEPI) is building a bank of potential vaccines for viral diseases, such as SARS and MERS (Middle East respiratory syndrome), that are not currently of commercial interest. CEPI's goal is to focus on the development or licensure and manufacturing of high-potential viral vaccines through early-stage human trials and to purchase small stockpiles to mitigate the next pandemic (Mullard 2016).

Medical supplies that may be needed for supportive care during a pandemic include hospital beds, disinfectants, ICU supplies (such as ventilators), and personal protective equipment (WHO 2015b).

Medical interventions for pandemic influenza include antiviral drugs and antibiotics to treat bacterial coinfections. Antivirals especially may reduce mortality when given within 48 hours of symptom onset (Domínguez-Cherit and others 2009; Jain and others 2009). However, because of delays in case identification and antiviral deployment (as discussed in box 17.2), LMICs may experience only limited benefits from antiviral drugs.

Potential for Scaling Up

The term *scaling up* refers to the expansion of health intervention coverage (Mangham and Hanson 2010). In the context of pandemic preparedness, successfully scaling up requires health systems to expand services to accommodate rapid increases in the number of suspected cases. Scaling up is facilitated by *surge capacity* (the ability to draw on additional clinical personnel, logisticians, and financial and other resources) as well as preexisting operational relationships and plans linking government, nongovernmental organizations, and the private sector. Ultimately, scaling up consists of having both local surge capacity and the absorptive capacity to accept outside assistance.

Local capacity building is vital, and some capacities may have particularly important positive externalities during outbreaks. During the 2014 Ebola importation into Nigeria, surge capacity that existed because of polio eradication efforts contributed to a more successful outbreak response (Yehualashet and others 2016). Key elements included national experience running an emergency operations center and the use of global positioning systems to support contact tracing (Shuaib and others 2014; WHO 2015a).

Stockpiling of vaccines, medicines (including antibiotics and antivirals), and equipment (such as masks, gowns, and ventilators) also can be useful for building local surge capacity (Dimitrov and others 2011; Jennings and others 2008; Morens, Taubenberger, and Fauci 2008; Radonovich and others 2009). During a pandemic, health systems can tap into stockpiles more quickly than they can procure supplies from external sources or boost production. However, there are five important considerations for keeping stockpiles:

- Building a stockpile requires significant up-front costs, which can be especially prohibitive for LICs (Oshitani, Kamigaki, and Suzuki 2008).
- Prepandemic vaccines may not be closely matched to the pathogen causing the pandemic.
- The optimal size of a stockpile can be challenging to determine.
- Stockpiles need to be refreshed regularly, because pharmaceuticals and equipment can reach expiration dates.
- Robust health systems and channels for disseminating and using the stockpiles also must exist.

Boosting local production capacity for necessary supplies may be a viable strategy for pandemic preparedness and may circumvent some of the challenges associated with amassing stockpiles.

The 2009 influenza pandemic demonstrated how scaling up can affect the success rate of a mass vaccination campaign (table 17.5). Vaccination rates increased according to country income level, suggesting that vaccination campaigns were most successful in HICs, likely because of the size of their stockpiles, increased manufacturing capacity for vaccines, increased availability of vaccines, and more streamlined logistics in vaccine deployment.

Building local capacity to scale up is challenging, especially in LMICs. The biggest challenges include infrastructural gaps (such as weak road, transportation, and communications networks) and shortfalls in human resources (such as logisticians, epidemiologists, and clinical staff). Bilateral and multilateral aid organizations have channeled substantial funding into building and sustaining local technical capacities in LMICs. This type of investment is critically important. But, particularly in LMICs with weak health system capacity, progress in expanding local surge capacity likely will be slow.

Another key component of scaling up, especially in LMICs, is the ability to use external assistance effectively.

Table 17.5 Vaccination Rates during the 2009 Influenza Pandemic, by Country Income Level

Country income level[a]	Number of countries with data	Share of population vaccinated (%)
Low-income	13	5.7
Middle-income	42	8.5
High-income	31	16.8

Sources: Mihigo and others 2012; Tizzoni and others 2012; WHO 2013b.
a. Income groups follow World Bank income classifications for fiscal 2018, based on estimates of 2016 gross national income per capita and calculated using the World Bank Atlas method: low-income (US$1,005 or less), middle-income (US$1,006–US$12,235), and high-income (US$12,236 or more). For further explanation, see https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.

During the 2014 West Africa Ebola epidemic, a surge of foreign clinicians, mobile medical units, and epidemiologists and other public health personnel was required to bolster limited local resources. LMICs can improve systems to facilitate and coordinate surges of foreign support in the following ways:

- Streamline customs processes for critical medical supplies and drugs.
- Establish mechanisms to coordinate the deployment and operations of foreign medical teams.
- Build mechanisms to coordinate between military and humanitarian units involved in crisis response.

Even so, local absorptive capacity (that is, the ability to channel and use foreign assistance effectively) has its limits. Constraints in bureaucratic capacity, financial controls, logistics, and infrastructure all are likely to be most severe in the countries that most need foreign assistance to manage infectious disease crises.

Furthermore, although external assistance is a viable strategy during localized epidemics, it has limitations that are likely to arise during large-scale pandemics. First, supply constraints exist, including limits to the number of medical personnel (especially those with crisis response and infectious disease competencies) and the number of specialized resources (such as integrated mobile medical clinics available for deployment).

Second, during a severe pandemic, countries are likely to use such resources locally before providing medical assistance abroad. The global humanitarian system provides a critical reservoir of crisis response capacity and shock absorption. However, the humanitarian system currently is straining under the pressure of other crises, including upsurges in violent conflict (Stoddard and others 2015). A severe epidemic or pandemic can quickly outstrip international resources. Médecins Sans Frontières (Doctors Without Borders), an international health organization with deep experience providing Ebola treatment, found itself "pushed to the limits and beyond" during the 2014 West Africa Ebola epidemic (MSF 2015).

Risk Transfer Mechanisms

As with any other type of natural disaster, the risk from pandemics cannot be eliminated. Despite prevention efforts, pandemics will continue to occur and will at times overwhelm the systems that have been put in place to mitigate their health, societal, and economic effects. The residual risk may be significant, particularly for LMICs that lack the resilience or resources to absorb shocks to public health and public finances. Risk transfer mechanisms (such as specialized insurance facilities) offer an additional tool to manage this risk.

Risk-based insurance products are increasingly deployed in LMICs to pay for remediation and reconstruction costs following natural catastrophes such as hurricanes, floods, and droughts (ARC 2016; IFRC 2016). Insurance products for epidemics and pandemics require specific characteristics. First, insurance policies should be designed to release discretionary funds early in the course of an outbreak. In situations where financing poses a constraint to mobilizing personnel, drugs, or other supplies, payouts can be used to mobilize a public health response and mitigate further spread of disease, reducing the potential health and economic impacts of the pandemic. Second, because pandemics do not stay contained in national borders, a strong case can be made for mobilizing bilateral and multilateral financing of LMICs' insurance premiums as a cost-effective way to improve global preparedness and support mitigation efforts. Third, risk transfer systems require the availability of rigorously and transparently compiled data to trigger a payout. In the context of pandemic insurance, the development of risk transfer systems requires countries to build the following capacities, among others:

- Robust surveillance data to identify when an outbreak has reached sufficient scale to require the release of funds
- Laboratory capacity to confirm the causative agent
- Predefined contingency and response plans to spend the funds effectively upon their release.

Insurance facilities can create positive incentives for LMICs to invest in planning and capacity building. Insurance mechanisms may have other positive externalities: most notably, the potential release of funds may provide a strong incentive for the timely reporting of surveillance data. However, insurance facilities also may introduce perverse incentives (including incentives to distort surveillance data) and potential moral hazards (such as permitting riskier activities). These incentive problems may be mitigated in the design of the risk transfer mechanism, such as by providing coverage only when minimum requirements for surveillance accuracy are met, by having preset phased triggers for payouts, and by including incentive payouts for successfully containing an outbreak.

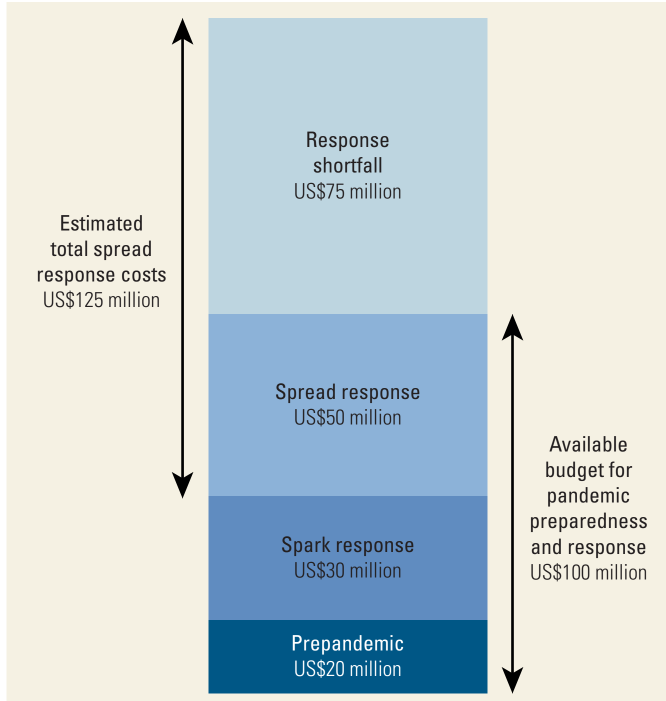
Relative to investments in basic health provision, building capacity in infectious disease surveillance systems and other dimensions of pandemic preparedness has uncertain and potentially distant benefits. In LICs where near-term health needs are acute, this can complicate the political and economic logic for investing in pandemic preparedness (Buckley and Pittluck 2016). The use of catastrophe modeling tools (such as EP curves) can clarify the benefit-cost rationale and the relevant time horizon for investments in preparedness, and it can inform the design and financial structure of pandemic insurance policies.

Figure 17.3 shows a country's hypothetical pandemic preparedness budget allocation and the portion of risk transfer in estimated total costs of spread response. In this example, a country has a total budget of US$100 million to cover all aspects of pandemic preparedness during the prepandemic, spark, and spread periods. After allocating half of the funds for prepandemic and spark response activities, US$50 million is left for pandemic spread response. On the basis of its risk tolerance, the country makes a decision to manage its risk at the 3 percent annual probability point on its EP curve. Modeling estimates indicate that a successful response to a pandemic at this level would require at least US$125 million, which would fund spread response activities, shown in box 17.1. Because only US$50 million is left after allocation to prepandemic and spark response activities, this would leave a shortfall of US$75 million. Some or all of this shortfall could be offloaded to another entity, such as a catastrophe risk insurance pool, which would give the country access to a payout during a pandemic.

Innovations in pandemic financing have been developed in response to the significant burden that a pandemic can place on a country's financial resources. One such innovation is the World Bank's Pandemic Emergency Financing Facility (PEF) (Katz and Seifman 2016).[3] A type of disaster risk pool, the PEF provides poorly resourced countries with an infusion of funds to help with the costs of response in the early stages of an epidemic or pandemic. The maximum total coverage over a three-year period is US$500 million. Notably, the US$500 million coverage is much lower than the estimated US$3.8 billion cost of the multinational response to the 2014 West Africa Ebola epidemic (USAID and CDC 2016). Because the PEF is designed to trigger early in an outbreak, the anticipated funding is less than would be required for a full-fledged response once a widespread pandemic is under way.

Risk transfer mechanisms such as insurance offer an injection of financial resources to help insured parties rapidly scale up disease response activities. As such, the utility of risk transfer mechanisms depends, in large part, on the absorptive capacity of the insured party. A country must have the ability to use insurance payouts effectively to access additional human resources

Figure 17.3 Hypothetical Pandemic Preparedness Budget and Response Shortfall, Which Could Be Managed via Risk Transfer Mechanisms



Source: Metabiota.
Note: Numbers are provided solely for illustrative purposes.

(clinicians, community health workers), personal protective equipment and other medical equipment consumables, and vaccines and therapeutics, from either domestic or international resources.

Adequacy of Evidence on Pandemics in LMICs

Much of the available data regarding pandemics (including the morbidity and mortality impacts of historical pandemics) and the effectiveness of different preparedness efforts and interventions come from HICs and upper-middle-income countries. Understanding of the prevalence of risk drivers, especially regarding spark risk, has improved markedly in both high- and low-income contexts. However, gaps in surveillance and reporting infrastructure in LMICs mean that, during a pandemic, many cases may never be detected or reported to the appropriate authorities (Katz and others 2012). Particularly in LICs, empirical data on outbreak occurrences may be biased downward systematically.

Additionally, the means to disseminate collected data rapidly may not exist. For example, data may be kept in paper archives, so resource-intensive digitization may be required to analyze and report data to a wider audience.

Data dissemination challenges are further compounded by a publication bias that results in overrepresentation of HICs in the scientific literature (Jones and others 2008).

SUMMARY OF PANDEMIC INTERVENTION COSTS AND COST-EFFECTIVENESS

Few data are available regarding costs and cost-effectiveness of pandemic preparedness and response measures, and they focus almost exclusively on HICs. The available data suggest that the greatest cost-related benefits in pandemic preparedness and response are realized from early recognition and mitigation of disease—that is, catching and stopping sparks before they spread. Costs can be reduced if action is taken before an outbreak becomes a pandemic. Similarly, once a pandemic has begun, preventing illness generally is more cost-effective than treating illness, especially because hospitalizations typically have the highest direct cost per person. High costs also may occur as a result of interventions (such as quarantines and school closures) that lead to economic disruption. These interventions may be more cost-effective during a severe pandemic.

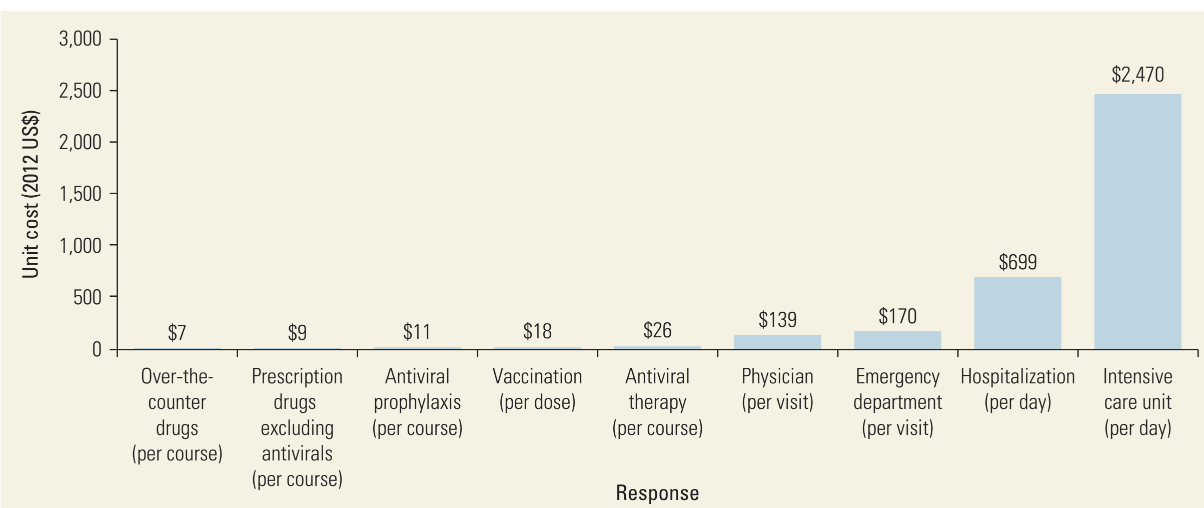
Program and Health System Costs

No systematic time-series data exist on global spending on pandemic preparedness, and arriving at an exact figure is complicated by the fact that many investments in building basic health system capacity also support core dimensions of pandemic preparedness. An analysis of global health spending found that roughly 1 percent of global ODA spending on health in 2013 (approximately US$204 million) focused specifically on pandemic preparedness (Schäferhoff and others 2015). Other, non-ODA spending on pandemic preparedness is similarly difficult to measure but likely to be significant; in 2013, the U.S. Department of Defense spent roughly US$256 million on efforts to build global biosurveillance and response capacities (KFF 2014).

Globally, the current funding for pandemic preparedness and response falls short of what is needed. In 2016, the international Commission on a Global Health Risk Framework for the Future recommended an additional US$4.5 billion annual global investment for upgrading pandemic preparedness at the country level, for funding infectious disease research and development efforts, and for establishing or replenishing rapid-response financing mechanisms such as the World Bank's PEF (Sands, Mundaca-Shah, and Dzau 2016).

Costs for efforts associated with prepandemic preparedness activities also are not well quantified, although investment in One Health activities is likely to be cost-effective (World Bank 2012). The USAID PREDICT project has estimated that discovery and detection of the majority of zoonotic viruses would cost US$1.6 billion (Anthony and others 2013). The Global Virome Project, a more comprehensive study aiming to characterize more than 99 percent of the world's viruses, is estimated to cost US$3.4 billion over 10 years (Daszak and others 2016). Building on efforts to identify and describe the ecology of potential pandemic viruses, the Coalition for

Figure 17.4 Unit Costs for Selected Influenza Pandemic Response Activities



Source: Based on Lugnér and Postma 2009.
Note: Includes studies from France, Israel, the Netherlands, Singapore, the United Kingdom, and the United States.

Epidemic Preparedness Innovations (CEPI) estimated a cost of US$1 billion over five years to develop vaccine candidates against known emerging infectious diseases (for example, Ebola virus) and to build technology platforms and production facilities to accelerate vaccine response to outbreaks of known or unknown pathogens (Brende and others 2017).

Instituting response measures after a pandemic has begun can be expensive, with most of the direct cost borne by the health care sector, although response costs typically are not reported in a cohesive manner. As noted, the response to the 2014 West Africa Ebola epidemic cost more than US$3.8 billion, including donations from several countries (USAID and CDC 2016). Additionally, the World Bank Group mobilized US$1.6 billion from the International Development Association and the International Finance Corporation to stimulate economic recovery in the three worst-affected countries of Guinea, Liberia, and Sierra Leone (World Bank 2016). Taken together, at US$5.4 billion, these values amount to a cost of US$235 per capita for these three countries.

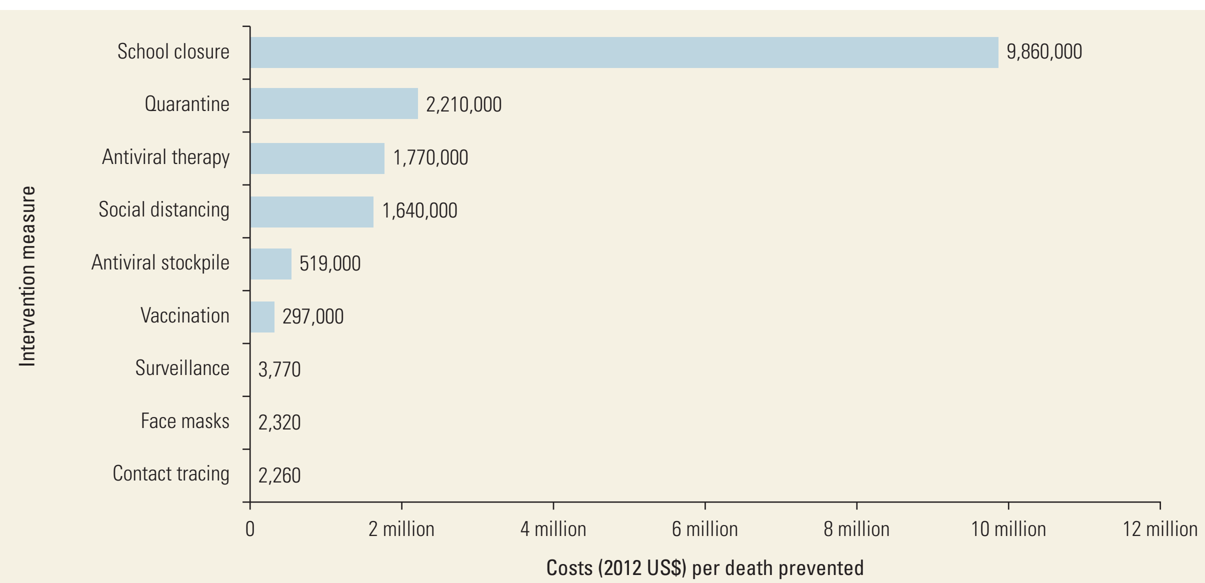
When total costs for response are not available, unit costs for response activities provide valuable insights. Figure 17.4 shows estimated unit costs for selected response measures, based on modeling studies for pandemic influenza in HICs. Vaccinations and medicines have the lowest unit costs; in LMICs, large-scale purchasing and subsidies could push drug costs down even more. Conversely, hospital care has the highest unit costs. Costs per day of hospitalization (especially those with ICU involvement) can add up quickly when aggregated at the national level. However, these medical care costs are potentially bounded by capacity limits (such as a finite number of hospital beds), especially during more severe pandemics.

Pandemic severity itself can play a role in the drivers of cost and the effects of mitigation efforts. One study based on modeling simulations in an Australian population found that, in low-severity pandemics, most costs borne by the larger economy (not just the health care system) come from productivity losses related to illness and social distancing. In higher-severity pandemics, the largest drivers of costs are hospitalization costs and productivity loss because of deaths (Milne, Halder, and Kelso 2013).

Costs per Death Prevented

Figure 17.5 depicts a compilation of data from 18 scientific publications that examined costs and benefits associated with response during the 2009 influenza pandemic. The lowest costs per deaths prevented were found for contact tracing, face masks, and surveillance. Pharmaceutical interventions such as vaccines and antiviral therapies were in the midrange.

Figure 17.5 Health Care System and Economic Costs per Death Prevented for Selected Interventions during the 2009 Influenza Pandemic



Source: Based on data from Pasquini-Descomps, Brender, and Maradan 2016.
Note: Includes studies from Australia, Brazil, Canada, China, Singapore, Sweden, the United Kingdom, and the United States.

Measures that decreased person-to-person contact, including social distancing, quarantine, and school closures, had the greatest cost per death prevented, most likely because of the amount of economic disruption caused by those measures. Social distancing includes avoidance of large gatherings and public places where economic activities occur. School closures often lead to lost productivity because they cause workplace absenteeism among caretakers of school-age children. Macroeconomic model simulations also have identified school closures as a potential source of GDP loss during a moderately severe pandemic (Smith and others 2009).

The information shown in figure 17.5 is subject to several caveats:

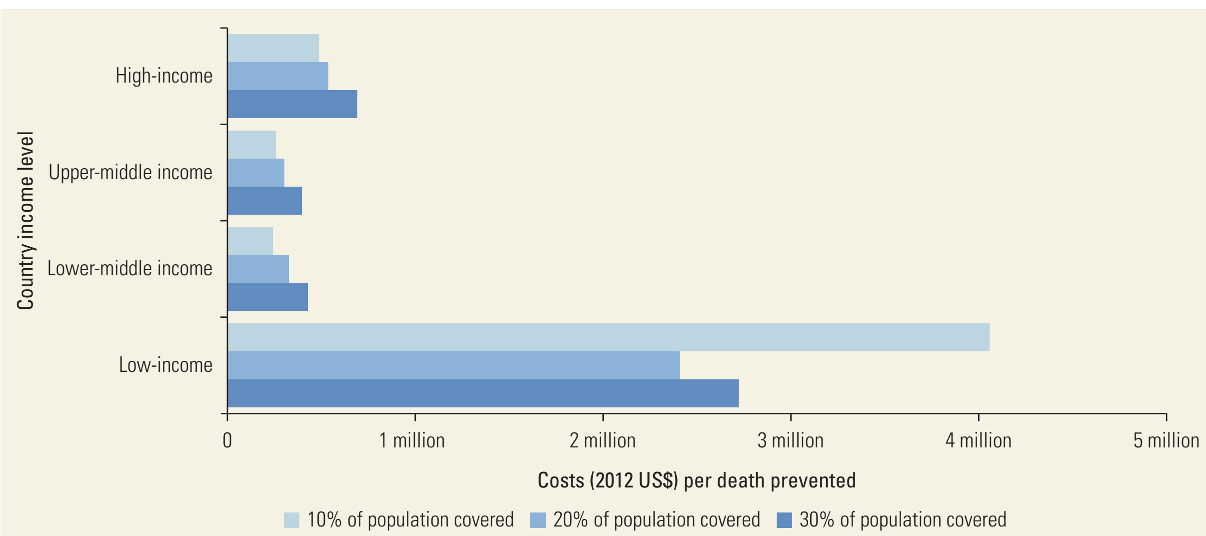
- The data come from only a few studies covering a handful of countries.
- Cost-utility analyses of pandemic preparedness and response for LMICs are rare. Because the underlying data for these studies were drawn primarily from HICs, the estimates may not accurately represent the relative benefit-cost of interventions in LMICs. For example, in countries with high unemployment and underemployment, school closures may not lead to increased workforce absenteeism and thus might have a lower cost per death prevented.
- The 2009 influenza pandemic is considered a relatively mild pandemic. In a more severe influenza pandemic, the cost per death prevented could decrease for some interventions, such as school closures.
- Results are sensitive to assumptions about the value of a prevented death and estimated costs of different interventions.
- The data cover only pandemics caused by influenza. For pandemics caused by other types of pathogens, the cost-utility values may be different, and not all intervention measures may be available.

Data on antiviral stockpiles provide some insight into how the cost utility of pandemic preparedness efforts may vary by country income level. Figure 17.6 shows the cost utility of antiviral stockpiling by country income level, based on simulation studies.

A more recent study found that antiviral stockpiling in Cambodia (a lower-middle-income country) would cost between US$3,584 and US$115,168 per death prevented; however, this result is highly sensitive to assumptions about the timing between pandemics (Drake, Chalabi, and Coker 2015).

Although based only on a handful of countries, the results suggest that antiviral stockpiling in LICs has an extremely high cost per death prevented, whereas countries at other income levels are clustered within much lower ranges. Antiviral stockpiling is not cost-effective or feasible for LICs, primarily because of the high cost of antiviral agents. For stockpiling to be a cost-effective

Figure 17.6 Cost Utility of Antiviral Stockpiling for Pandemic Influenza Preparedness, by Share of Population Covered and Country Income Level, 2011



Source: Based on data from Carrasco and others 2011.
Note: Includes data from one low-income country (Zimbabwe), three lower-middle-income countries (Guatemala, India, and Indonesia), two upper-middle-income countries (Brazil and China), and four high-income countries (New Zealand, Singapore, the United Kingdom, and the United States).

strategy for LICs, almost all of the costs would have to be subsidized. The associated costs also may be reduced by the increased availability of generic antiviral drugs. Additionally, the efficacy of antivirals is not assured, particularly for LICs, which may not be able to identify cases early enough to administer antivirals efficaciously.

Cost-Effectiveness

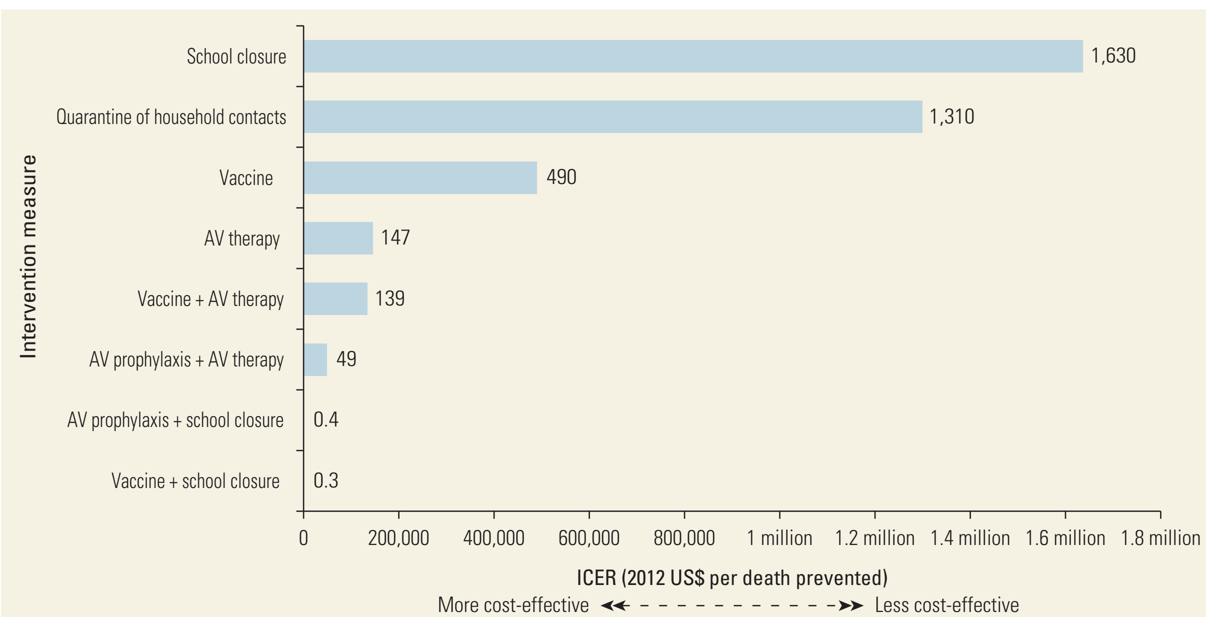
Pérez Velasco and others (2012) synthesized information from 44 studies that contained economic evaluations of influenza pandemic preparedness and response strategies in HICs (figure 17.7). In their analysis, the following interventions among the general population had the potential to provide cost savings: vaccines, antiviral treatment, social distancing, antiviral prophylaxis plus antiviral treatment, and vaccines plus antiviral treatment. The cost savings from antiviral drugs found in this study are likely to be diminished in LMICs, as inability to deploy antivirals in a timely manner poses a serious challenge to their efficacious use.

Depending on the characteristics of a pandemic and how mitigation efforts are implemented, some mitigation strategies could become highly cost-*ineffective*. For example, a costly vaccination campaign that is carried out in an area well after a pandemic peaks is not nearly as effective in reducing transmission as having vaccines available and distributed earlier in the pandemic.

Allocation of limited resources (by creating priority groups for vaccines and antivirals) is an important consideration during a pandemic. Modeling studies from the 2009 influenza pandemic investigated the most cost-effective strategies for allocating vaccines. Those studies found that vaccinating high-risk individuals was more cost-effective than prioritizing children. Favoring children decreased the overall infection rate, but high-risk individuals were the predominant drivers of direct costs during the pandemic, because they were more likely to be hospitalized (Lee and others 2010). However, these studies did not account for the indirect costs of school closures and absenteeism. Consideration of these factors could reveal increased cost savings from vaccinating children.

Another key question for benefit-cost analyses related to pandemics is the extent to which stockpiles of vaccines, antiviral drugs, and protective equipment should be assembled in advance of a pandemic. Vaccines for a novel influenza virus can take several months to develop, and vaccines for other pathogens (for example, Ebola and Zika) can take even longer to develop. Studies have examined the cost-effectiveness of stockpiling prepandemic vaccines that have lower efficacy than reactive vaccines but can be deployed

Figure 17.7 Cost-Effectiveness of Selected Interventions for Pandemic Influenza Preparedness and Response in High-Income Countries



Source: Based on Pérez Velasco and others 2012.
Note: AV = antiviral; ICER = incremental cost-effectiveness ratio.

more quickly. One study found that cost savings can be obtained as long as prepandemic vaccines have at least 30 percent efficacy. However, cost-effectiveness differs by pandemic severity and the percentage of the population that receives the vaccine during the vaccination campaign (Halder, Kelso, and Milne 2014).

Antiviral drugs to fight pandemic influenza also can be stockpiled ahead of time. However, the optimal number of doses to stockpile depends on factors including the effectiveness of concurrent interventions and the likelihood of antiviral wastage on noninfluenza respiratory infections (Greer and Schanzer 2013).

Most pandemic-related benefit-cost studies focus on pharmaceutical interventions for high-income and upper-middle-income countries. The studies have largely neglected the question of how to allocate strained resources in low- and lower-middle-income countries. Furthermore, few evaluations have been conducted of the cost-effectiveness of general investment in health systems, infrastructure, and capacity building as a means to achieve pandemic preparedness (Drake, Chalabi, and Coker 2012).

CONCLUSIONS AND RECOMMENDATIONS FOR PRIORITIZING INVESTMENTS TO MITIGATE PANDEMIC RISK IN RESOURCE-LIMITED SETTINGS

Preparing for a pandemic is challenging because of a multitude of factors, many of which are unique among natural disasters. Pandemics are rare events, and the risk of occurrence is influenced by anthropogenic changes in the natural environment. In addition, accountability for preparedness is diffuse, and many of the countries at greatest risk have the most limited capacity to manage and mitigate pandemic risk.

Unlike most other natural disasters, pandemics do not remain geographically contained, and damages can be mitigated significantly through prompt intervention. As a result, there are strong ethical and global health imperatives for building capacity to detect and respond to pandemic threats, particularly in countries with weak preparedness and high spark and spread risk.

Investments to improve pandemic preparedness may have fewer immediate benefits, particularly relative to other pressing health needs in countries with heavy burdens of endemic disease. Therefore, characterizing pandemic risk and identifying gaps in pandemic preparedness are essential for prioritizing and targeting capacity-building efforts. Thinking about risks in terms of frequency and severity, notably using probabilistic modeling and EP curves, can quantify the potential pandemic risks facing each country and clarify the benefit-cost case for investing in pandemic preparedness.

No single, optimal response to a public health emergency exists; strategies must be tailored to the local context and to the severity and type of pandemic. However, overarching lessons emerge after multiple regional epidemics and global pandemics. For example, because of their high spark and spread risks, many LMICs would benefit most from building situational awareness and health care coordination capacity; public health response measures are far more cost-effective if they are initiated quickly and if scarce resources are targeted appropriately.

Building pandemic situational awareness is complex, requiring coordination across bureaucracies, across the public and private sectors, and across disciplines with different training and different norms (including epidemiology, clinical medicine, logistics, and disaster response). However, an appropriately sized and trained health workforce (encompassing doctors, nurses, epidemiologists, veterinarians, laboratorians, and others) that is supported by adequate coordination systems is a fundamental need—the World Health Organization has recommended a basic threshold of 23 skilled health professionals per 10,000 people (WHO 2013a).

Increasing the trained health workforce also will increase the capacity to detect whether any particular population (for example, human, farm animal, or wildlife) is suffering from a pathogen with high pandemic risk. Increasing the health workforce also will improve the overall resiliency of the health system, an improvement that can be applied to any emergency that results in morbidity and mortality shocks.

Additionally, building situational awareness will require sustained investment in infectious disease surveillance, crisis management, and risk communications systems. Investments in these capacities are likely to surge after pandemic or epidemic events and then abate as other priorities emerge. Hence, stable investment to build sustained capacity is critical.

Risk transfer mechanisms such as catastrophe risk pools offer a viable strategy for countries to manage pandemic risk. Further developing these mechanisms will allow countries to offload portions of pandemic risk and response that are beyond their immediate budgetary capacity. For this reason, risk transfer solutions should be designed with the needs and constraints of LMICs in mind. However, countries must have predefined contingency and response plans as well as the absorptive capacity to use the emergency financing offered by such solutions. Broad and effective use of pandemic insurance will require parallel investments in capacity building and emergency response planning.

Finally, researchers must address the significant knowledge gaps that exist regarding LMICs' pandemic preparedness and response. Improving the tracking of spending and aid flows specifically tied to pandemic prevention and preparedness is vital to tracking gaps and calibrating aid flows for maximum efficiency. Systematic data on response costs in low-income settings are scarce, including data regarding spending on clinical facilities, supplies, human resources, and response activities such as quarantines. Bridging these data gaps can improve pandemic preparedness planning and response through evidence-based decision making and support efforts to prevent and mitigate epidemics and pandemics.

ACKNOWLEDGMENTS

The authors would like to thank Ron Waldman, Dean Jamison, Steve Morse, Peter Sands, Mukesh Chawla and the Secretariat of the International Working Group on Financing Preparedness, Kimberly Dodd, Mary Guttieri, Patrick Ayscue, Damien Joly, Sarah Barthel, Joseph Krilanovich, Jonathan Koshi, Mike Gahan, Kierste Miller, Cathine Lam, Catherine Planey, Nicole Stephenson, Volodymyr Serhiyenko, Ming Yii Goh, Alessandro Vespignani, Qian Zhang, Matteo Chinazzi, Ana Pastore y Piontti, Marco Schäferhoff, and Jessica Kraus for their valuable technical and editorial contributions to the chapter.

NOTES

This chapter uses World Bank Income Classifications for 2018 as follows, based on estimates of gross national income (GNI) per capita for 2015:

- Low-income countries (LICs) = US$1,005 or less
- Middle-income countries (MICs) are subdivided:
  - (a) lower-middle-income = US$1,006 to US$3,995
  - (b) upper-middle-income countries (UMICs) = US$3,996 to US$12,235
- High-income countries (HICs) = US$12,236 or more.

1. One Health considers individual, community, and animal health as interconnected and requires the collaboration of human, animal, and environmental health professionals to recognize and alleviate the problems on one level to reduce the downstream health effects on another level (for example, rabies in animals and humans). For more information, see the U.S. Centers for Disease Control and Prevention's webpage, https://www.cdc.gov/onehealth/basics/index.html.
2. PREDICT, a project of USAID's Emerging Pandemic Threats Program, was initiated in 2009 to strengthen global capacity for detection and discovery of zoonotic viruses with pandemic potential. Working with partners in 31 countries, PREDICT is building platforms for conducting disease surveillance and for identifying and monitoring pathogens that can be shared between animals and people. Using the One Health approach, the project is investigating the behaviors, practices, and ecological and biological factors driving the emergence, transmission, and spread of disease. For more information, see the project website, http://www.vetmed.ucdavis.edu/ohi/predict/.
3. For more information about the PEF, see the brief on the World Bank website, "Pandemic Emergency Financing Facility: Frequently Asked Questions," http://www.worldbank.org/en/topic/pandemics/brief/pandemic-emergency-facility-frequently-asked-questions.

REFERENCES

Achonu, C., A. Laporte, and M. A. Gardam. 2005. "The Financial Impact of Controlling a Respiratory Virus Outbreak in a Teaching Hospital: Lessons Learned from SARS." *Canadian Journal of Public Health* 96 (1): 52–54.

Anthony, S. J., J. H. Epstein, K. A. Murray, I. Navarrete-Macias, C. M. Zambrana-Torrelio, and others. 2013. "A Strategy to Estimate Unknown Viral Diversity in Mammals." *MBio* 4 (5): e00598-13.

Arabi, Y. M., H. H. Balkhy, F. G. Hayden, A. Bouchama, T. Luke, and others. 2017. "Middle East Respiratory Syndrome." *New England Journal of Medicine* 376 (6): 584–94.

ARC (African Risk Capacity). 2016. "African Risk Capacity Strategic Framework 2016–2020." Strategy and policy document, ARC, Johannesburg, South Africa.

Arimah, B. C. 2010. "The Face of Urban Poverty: Explaining the Prevalence of Slums in Developing Countries." In *Urbanization and Development: Multidisciplinary Perspectives*, edited by Jo Beall, Basudeb Guha-Khasnobis, and Ravi Kanbur, 143–64. Oxford: Oxford University Press.

ASPR (Assistant Secretary for Preparedness and Response). 2014. "Public Health and Medical Situational Awareness Strategy." Strategy document for situational awareness implementation plan, U.S. Department of Health and Human Services, Washington, DC.

Aylward, B., P. Barboza, L. Bawo, E. Bertherat, P. Bilivogui, and others. 2014. "Ebola Virus Disease in West Africa—The First 9 Months of the Epidemic and Forward Projections." *New England Journal of Medicine* 371 (16): 1481–95.

Barden-O'Fallon, J., M. A. Barry, P. Brodish, and J. Hazerjian. 2015. "Rapid Assessment of Ebola-Related Implications for Reproductive, Maternal, Newborn, and Child Health Service Delivery and Utilization in Guinea." *PLoS Currents Outbreaks* (August): 7. doi:10.1371/currents.outbreaks.0b0ba06009dd091bc39ddb3c6d7b0826.

Barrett, R., and P. J. Brown. 2008. "Stigma in the Time of Influenza: Social and Institutional Responses to Pandemic

Emergencies." *Journal of Infectious Diseases* 197 (Suppl 1): S34–S37.

Bedrosian, S. R., C. E. Young, L. A. Smith, J. D. Cox, C. Manning, and others. 2016. "Lessons of Risk Communication and Health Promotion—West Africa and United States." *Morbidity and Mortality Weekly Report (MMWR) Supplements* 65 (3): 68–74.

Bootsma, M. C. J., and N. M. Ferguson. 2007. "The Effect of Public Health Measures on the 1918 Influenza Pandemic in U.S. Cities." *Proceedings of the National Academy of Sciences of the United States of America* 104 (18): 7588–93.

Brattberg, E., and M. Rhinard. 2011. "Multilevel Governance and Complex Threats: The Case of Pandemic Preparedness in the European Union and the United States." *Global Health Governance* 5 (1): 1–21.

Brende, B., J. Farrar, D. Gashumba, C. Moedas, T. Mundel, and others. 2017. "CEPI—A New Global R&D Organisation for Epidemic Preparedness and Response." *The Lancet* 389 (10066): 233–35.

Brundage, J. F., and G. D. Shanks. 2008. "Deaths from Bacterial Pneumonia during 1918–19 Influenza Pandemic." *Emerging Infectious Diseases* 14 (8): 1193–99.

Buckley, G. J., and R. E. Pittluck. 2016. *Global Health Risk Framework: Pandemic Financing: Workshop Summary.* Washington, DC: National Academies Press.

Burns, A., D. Van der Mensbrugghe, and H. Timmer. 2006. "Evaluating the Economic Consequences of Avian Influenza." Working Paper 47417, World Bank, Washington, DC.

Carrasco, L. R., V. J. Lee, M. I. Chen, D. B. Matchar, J. P. Thompson, and others. 2011. "Strategies for Antiviral Stockpiling for Future Influenza Pandemics: A Global Epidemic-Economic Perspective." *Journal of the Royal Society Interface* 8 (62): 1307–13.

Chan, E. H., T. F. Brewer, L. C. Madoff, M. P. Pollack, A. L. Sonricker, and others. 2010. "Global Capacity for Emerging Infectious Disease Detection." *Proceedings of the National Academy of Sciences of the United States of America* 107 (50): 21701–6.

Chandy, L., H. Kato, and H. Kharas, eds. 2015. *The Last Mile in Ending Extreme Poverty*. Washington, DC: Brookings Institution Press.

Charu, V., G. Chowell, L. S. Palacio Mejia, S. Echevarría-Zuno, V. H. Borja-Aburto, and others. 2011. "Mortality Burden of the A/H1N1 Pandemic in Mexico: A Comparison of Deaths and Years of Life Lost to Seasonal Influenza." *Clinical Infectious Diseases* 53 (10): 985–93.

Chisholm, H. 1911. "Cholera." *Encyclopedia Britannica* 11 (6): 265–66.

Cohen, N. J., C. M. Brown, F. Alvarado-Ramy, H. Bair-Drake, G. A. Benenson, and others. 2016. "Travel and Border Health Measures to Prevent the International Spread of Ebola." *Morbidity and Mortality Weekly Report (MMWR) Supplements* 65 (3): 57–67.

Cohn, S. K. 2007. "The Black Death and the Burning of Jews." *Past and Present* 196 (1): 3–36.

Colizza, V., A. Barrat, M. Barthelemy, A. J. Valleron, and A. Vespignani. 2007. "Modeling the Worldwide Spread of Pandemic Influenza: Baseline Case and Containment Interventions." *PLoS Medicine* 4 (1): 95–110.

Daszak, P., D. Carroll, N. Wolfe, and J. Mazet. 2016. "The Global Virome Project." *International Journal of Infectious Diseases* 53 (Suppl): 36.

Dawood, F. S., A. D. Iuliano, C. Reed, M. I. Meltzer, D. K. Shay, and others. 2012. "Estimated Global Mortality Associated with the First 12 Months of 2009 Pandemic Influenza A H1N1 Virus Circulation: A Modelling Study." *The Lancet Infectious Diseases* 12 (9): 687–95.

de Wit, E., D. Falzarano, C. Onyango, K. Rosenke, A. Marzi, and others. 2016. "The Merits of Malaria Diagnostics during an Ebola Virus Disease Outbreak." *Emerging Infectious Diseases* 22 (2): 323–26.

DeWitte, S. N. 2014. "Mortality Risk and Survival in the Aftermath of the Medieval Black Death." *PLoS One* 9 (5): e96513.

Diamond, J. 2009. *Guns, Germs, and Steel: The Fates of Human Societies*. New York: Norton.

Dimitrov, N., S. Goll, N. Hupert, B. Pourbohloul, and L. Meyers. 2011. "Optimizing Tactics for Use of the U.S. Antiviral Strategic National Stockpile for Pandemic Influenza." *PloS One* 6 (1): e16094.

Dixon, S., S. McDonald, and J. Roberts. 2001. "AIDS and Economic Growth in Africa: A Panel Data Analysis." *Journal of International Development* 13 (4): 411–26.

Domínguez-Cherit, G., S. E. Lapinsky, A. E. Macias, R. Pinto, L. Espinosa-Perez, and others. 2009. "Critically Ill Patients with 2009 Influenza A(H1N1) in Mexico." *Journal of the American Medical Association* 302 (17): 1880–87.

Drake, T. L., Z. Chalabi, and R. Coker. 2012. "Cost-Effectiveness Analysis of Pandemic Influenza Preparedness: What's Missing?" *Bulletin of the World Health Organization* 90 (12): 940–41.

———. 2015. "Buy Now, Saved Later? The Critical Impact of Time-to-Pandemic Uncertainty on Pandemic Cost-Effectiveness Analyses." *Health Policy and Planning* 30 (1): 100–10.

Elbe, S. 2002. "HIV/AIDS and the Changing Landscape of War in Africa." *International Security* 27 (2): 159–77.

Epstein, H. 2014. "Ebola in Liberia: An Epidemic of Rumors." *New York Review of Books* 61 (20): 91–95.

Evans, D. K., M. Goldstein, and A. Popova. 2015. "Health-Care Worker Mortality and the Legacy of the Ebola Epidemic." *The Lancet Global Health* 3 (8): e439–e440.

Falcone, R. E., and A. Detty. 2015. "The Next Pandemic: Hospital Response." *Emergency Medical Reports* 36 (26): 1–16.

Fan, V. Y., D. T. Jamison, and L. S. Summers. 2016. "The Inclusive Cost of Pandemic Influenza Risk." NBER Working Paper 22137, National Bureau of Economic Research, Cambridge, MA.

Farmer, P. 1996. "Social Inequalities and Emerging Infectious Diseases." *Emerging Infectious Diseases* 2 (4): 259–69.

Fearon, J. D., and D. D. Laitin. 2003. "Ethnicity, Insurgency, and Civil War." *American Political Science Review* 97 (1): 75–90.

Ferguson, N. M., D. A. T. Cummings, S. Cauchemez, C. Fraser, S. Riley, and others. 2005. "Strategies for Containing an Emerging Influenza Pandemic in Southeast Asia." *Nature* 437 (7056): 209–14.

Fischer, J. E., and R. Katz. 2013. "Moving Forward to 2014: Global IHR (2005) Implementation." *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* 11 (2): 153–56.

Flahault, A., and A. J. Valleron. 1990. "HIV and Travel, No Rationale for Restrictions." *The Lancet* 336 (8724): 1197–98.

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.

Frieden, N. M. 1977. "The Russian Cholera Epidemic, 1892–93, and Medical Professionalization." *Journal of Social History* 10 (4): 538.

Fullam, J. D., and N. Madhav. 2015. "Quantifying Pandemic Risk." *The Actuary* 12 (1): 29–34.

Gilbert, M., N. Golding, H. Zhou, G. R. W. Wint, T. P. Robinson, and others. 2014. "Predicting the Risk of Avian Influenza A H7N9 Infection in Live-Poultry Markets across Asia." *Nature Communications* 5 (May): 1–7.

Greenhill, K., and B. Oppenheim. 2017. "Rumor Has It: The Adoption of Unverified Information in Conflict Zones." *International Studies Quarterly* 61 (3).

Greer, A. L., and D. Schanzer. 2013. "Using a Dynamic Model to Consider Optimal Antiviral Stockpile Size in the Face of Pandemic Influenza Uncertainty." *PLoS One* 8 (6): e67253.

Halder, N., J. K. Kelso, and G. J. Milne. 2014. "A Model-Based Economic Analysis of Pre-Pandemic Influenza Vaccination Cost-Effectiveness." *BMC Infectious Diseases* 14 (1): 266–85.

Henao-Restrepo, A. M., A. Camacho, I. M. Longini, C. H. Watson, W. J. Edmunds, and others. 2016. "Efficacy and Effectiveness of an rVSV-Vectored Vaccine in Preventing Ebola Virus Disease: Final Results from the Guinea Ring Vaccination, Open-Label, Cluster-Randomised Trial (Ebola Ça Suffit!)." *The Lancet* 389 (10068): 505–18.

Herstein, J. J., P. D. Biddinger, C. S. Kraft, L. Saiman, S. G. Gibbs, and others. 2016. "Initial Costs of Ebola Treatment Centers in the United States." *Emerging Infectious Diseases* 22 (2): 350.

Hollingsworth, T. D., N. M. Ferguson, and R. M. Anderson. 2006. "Will Travel Restrictions Control the International Spread of Pandemic Influenza?" *Nature Medicine* 12 (5): 497–99.

Hooghe, L., and G. Marks. 2003. "Unraveling the Central State, but How? Types of Multi-Level Governance." *American Political Science Review* 97 (2): 233–43.

ICG (International Crisis Group). 2015. *The Politics behind the Ebola Crisis*. Crisis Group Africa Report 232, International Crisis Group, Brussels, October 28.

IFRC (International Federation of Red Cross and Red Crescent Societies). 2016. *World Disasters Report, Resilience: Saving Lives Today, Investing for Tomorrow*. Geneva: IFRC.

Jain, S., L. Kamimoto, A. M. Bramley, A. M. Schmitz, S. R. Benoit, and others. 2009. "Hospitalized Patients with 2009 H1N1 Influenza in the United States, April–June 2009." *New England Journal of Medicine* 361 (20): 1935–44.

Jefferson, T., M. Jones, P. Doshi, E. A. Spencer, I. Onakpoya, and others. 2014. "Oseltamivir for Influenza in Adults and Children: Systematic Review of Clinical Study Reports and Summary of Regulatory Comments." *British Medical Journal* 348 (April): g2545.

Jennings, L. C., A. A. Monto, P. K. Chan, T. D. Szucs, and K. G. Nicholson. 2008. "Stockpiling Prepandemic Influenza Vaccines: A New Cornerstone of Pandemic Preparedness Plans." *The Lancet Infectious Diseases* 8 (10): 650–58.

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.

Jonas, O. B. 2013. "Pandemic Risk." Background paper for *World Development Report 2014: Risk and Opportunity; Managing Risk for Development*, World Bank, Washington, DC.

Jones, D. S. 2006. "The Persistence of American Indian Health Disparities." *American Journal of Public Health* 96 (12): 2122–34.

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

Jun, K. 2015. "MERS Outbreak Prompts South Korean Stimulus Package." *Wall Street Journal,* June 25.

Katz, M. A., B. D. Schoub, J. M. Heraud, R. F. Breiman, M. K. Njenga, and others. 2012. "Influenza in Africa: Uncovering the Epidemiology of a Long-Overlooked Disease." *Journal of Infectious Diseases* 26 (Suppl 1): S1–S4.

Katz, R. 2009. "Use of Revised International Health Regulations during Influenza A (H1N1) Epidemic, 2009." *Emerging Infectious Diseases* 15 (8): 1165–70.

Katz, R., and R. Seifman. 2016. "Opportunities to Finance Pandemic Preparedness." *The Lancet Global Health* 4 (11): e782–e783.

Kavet, J. 1977. "A Perspective on the Significance of Pandemic Influenza." *American Journal of Public Health* 67 (11): 1063–70.

Kelly, H. A., P. C. Priest, G. N. Mercer, and G. K. Dowse. 2011. "We Should Not Be Complacent about Our Population-Based Public Health Response to the First Influenza Pandemic of the 21st Century." *BMC Public Health* 11 (1): 78.

Keogh-Brown, M. R., and R. D. Smith. 2008. "The Economic Impact of SARS: How Does the Reality Match the Predictions?" *Health Policy* 88 (1): 110–20.

KFF (Henry J. Kaiser Family Foundation). 2014. "The U.S. Government and Global Emerging Infectious Disease Preparedness and Response." Fact sheet, December 8, http://kff.org/global-health-policy/fact-sheet/the-u-s-government-global-emerging-infectious-disease-preparedness-and-response/.

Kim, Y.-W., S.-J. Yoon, and I.-H. Oh. 2013. "The Economic Burden of the 2009 Pandemic H1N1 Influenza in Korea." *Scandinavian Journal of Infectious Diseases* 45 (5): 390–96.

Kozlowski, R. T., and S. B. Mathewson. 1997. "A Primer on Catastrophe Modeling." *Journal of Insurance Regulation* 15 (3): 322.

Lee, B. Y., S. T. Brown, G. W. Korch, P. C. Cooley, R. K. Zimmerman, and others. 2010. "A Computer Simulation of Vaccine Prioritization, Allocation, and Rationing during the 2009 H1N1 Influenza Pandemic." *Vaccine* 28 (31): 4875–79.

Lugnér, A. K., and M. J. Postma. 2009. "Mitigation of Pandemic Influenza: Review of Cost-Effectiveness Studies." *Expert Review of Pharmacoeconomics and Outcomes Research* 9 (6): 547–58.

Mackowiak, P. A., and P. S. Sehdev. 2002. "The Origin of Quarantine." *Clinical Infectious Diseases* 35 (9): 1071–72.

Mancini, S., M. E. Coldiron, A. Ronsse, B. K. Ilunga, K. Porten, and others. 2014. "Description of a Large Measles Epidemic in Democratic Republic of Congo, 2010–2013." *Conflict and Health* 8 (1): 9.

Mangham, L. J., and K. Hanson. 2010. "Scaling Up in International Health: What Are the Key Issues?" *Health Policy and Planning* 25 (2): 85–96.

Mathews, J. D., J. M. Chesson, J. M. McCaw, and J. McVernon. 2009. "Understanding Influenza Transmission, Immunity, and Pandemic Threats." *Influenza and Other Respiratory Viruses* 3 (4): 143–49.

McCoy, T. 2014. "Why the Brutal Murder of Several Ebola Workers May Hint at More Violence to Come." *Washington Post*, September 19.

McKibbin, W. J., and A. A. Sidorenko. 2006. "Global Macroeconomic Consequences of Pandemic Influenza." Analysis, Lowy Institute for International Policy, Sydney, Australia.

Mihigo, R., C. V. Torrealba, K. Coninx, D. Nshimirimana, M. P. Kieny, and others. 2012. "2009 Pandemic Influenza A Virus Subtype H1N1 Vaccination in Africa—Successes and Challenges." *Journal of Infectious Diseases* 206 (Suppl 1): S22–S28.

Milián, E., and A. A. Kamen. 2015. "Current and Emerging Cell Culture Manufacturing Technologies for Influenza Vaccines." *BioMed Research International* 2015 (1): 1–11.

Miller, M. A., C. Viboud, D. R. Olson, R. F. Grais, M. A. Rabaa, and others. 2008. "Prioritization of Influenza Pandemic Vaccination to Minimize Years of Life Lost." *Journal of Infectious Diseases* 198 (3): 305–11.

Milne, G. J., N. Halder, and J. K. Kelso. 2013. "The Cost-Effectiveness of Pandemic Influenza Interventions: A Pandemic Severity Based Analysis." *PLoS One* 8 (4): e61504.

Moon, S., D. Sridhar, M. A. Pate, J. K. Jha, C. Clinton, and others. 2015. "Will Ebola Change the Game? Ten Essential Reforms before the Next Pandemic. The Report of the Harvard–LSHTM Independent Panel on the Global Response to Ebola." *The Lancet* 386 (10009): 2204–21.

Morens, D. M., J. K. Taubenberger, and A. S. Fauci. 2008. "Predominant Role of Bacterial Pneumonia as a Cause of Death in Pandemic Influenza: Implications for Pandemic Influenza Preparedness." *Journal of Infectious Diseases* 198 (7): 962–70.

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.

Morse, S. S. 1995. "Factors in the Emergence of Infectious Diseases." *Emerging Infectious Diseases* 1 (1): 7–15.

Morse, S. S., J. A. K. Mazet, M. Woolhouse, C. R. Parrish, D. Carroll, and others. 2012. "Prediction and Prevention of the Next Pandemic Zoonosis." *The Lancet* 380 (9857): 1956–65.

MSF (Médecins Sans Frontières). 2015. *Pushed to the Limit and Beyond: A Year into the Largest Ever Ebola Outbreak*. Report, MSF, London.

Mullard, A. 2016. "New Vaccine Coalition Targets Epidemics." *Nature Reviews Drug Discovery* 15 (10): 669.

Murphy, F. A. 1998. "Emerging Zoonoses." *Emerging Infectious Diseases* 4 (3): 429–35.

Murray, C. J., A. D. Lopez, B. Chin, D. Feehan, and K. H. Hill. 2006. "Estimation of Potential Global Pandemic Influenza Mortality on the Basis of Vital Registry Data from the 1918–20 Pandemic: A Quantitative Analysis." *The Lancet* 368 (9554): 2211–18.

Nannei, C., S. Goldin, G. Torelli, H. Fatima, K. Kumar, and others. 2016. "Stakeholders' Perceptions of 10 Years of the Global Action Plan for Influenza Vaccines (GAP)—Results from a Survey." *Vaccine* 34 (45): 5393–99.

Neiderud, C.-J. 2015. "How Urbanization Affects the Epidemiology of Emerging Infectious Diseases." *Infection Ecology and Epidemiology* 5: 27060. doi:/10.3402/iee.v5.27060.

Oppenheim, B., M. D. Gallivan, N. Madhav, N. Brown, V. Serhiyenko, and others. 2017. "Global Preparedness for the Next Pandemic." Unpublished manuscript.

Oshitani, H., T. Kamigaki, and A. Suzuki. 2008. "Major Issues and Challenges of Influenza Pandemic Preparedness in Developing Countries." *Emerging Infectious Diseases* 14 (6): 875–80.

Osterholm, M. T. 2005. "Preparing for the Next Pandemic." *New England Journal of Medicine* 352 (18): 1839–42.

Paez-Espino, D., E. A. Eloe-Fadrosh, G. A. Pavlopoulos, A. D. Thomas, M. Huntemann, and others. 2016. "Uncovering Earth's Virome." *Nature* 536 (7617): 425–30.

Park, J., and J. Kim. 2015. "Hong Kong Sets 'Serious' Response to South Korea's MERS Outbreak." Reuters, June 8.

Parpia, A. S., M. L. Ndeffo-Mbah, N. S. Wenzel, and A. P. Galvani. 2016. "Effects of Response to 2014–2015 Ebola Outbreak on Deaths from Malaria, HIV/AIDS, and Tuberculosis, West Africa." *Emerging Infectious Diseases* 22 (3): 433–41.

Parveen, S., M. S. Islam, M. Begum, M. Alam, H. M. S. Sazzad, and others. 2016. "It's Not Only What You Say, It's Also How You Say It: Communicating Nipah Virus Prevention Messages during an Outbreak in Bangladesh." *BMC Public Health* 16 (1): 726–37.

Pasquini-Descomps, H., N. Brender, and D. Maradan. 2016. "Value for Money in H1N1 Influenza: A Systematic Review of the Cost-Effectiveness of Pandemic Interventions." *Value in Health* 20 (6): 819–27.

Pathmanathan, I., K. A. O'Connor, M. L. Adams, C. Y. Rao, P. H. Kilmarx, and others. 2014. "Rapid Assessment of Ebola Infection Prevention and Control Needs—Six Districts, Sierra Leone, October 2014." *Morbidity and Mortality Weekly Report (MMWR)* 63 (49): 1172–74.

Pérez Velasco, R., N. Praditsitthikorn, K. Wichmann, A. Mohara, S. Kotirum, and others. 2012. "Systematic Review of Economic Evaluations of Preparedness Strategies and Interventions against Influenza Pandemics." *PloS One* 7 (2): e30333.

Person, B., F. Sy, K. Holton, B. Govert, A. Liang, and others. 2004. "Fear and Stigma: The Epidemic within the SARS Outbreak." *Emerging Infectious Diseases* 10 (2): 358–63.

Pike, B. L., K. E. Saylors, J. N. Fair, M. Lebreton, U. Tamoufe, and others. 2010. "The Origin and Prevention of Pandemics." *Clinical Infectious Diseases* 50 (12): 1636–40.

Platt, C. 2014. *King Death: The Black Death and Its Aftermath in Late-Medieval England*. Oxon, U.K.: Routledge.

Porta, M., ed. 2014. *A Dictionary of Epidemiology*. 6th ed. Oxford: Oxford University Press.

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

———. 2009. *Contagion and Chaos: Disease, Ecology, and National Security in the Era of Globalization*. Cambridge, MA: MIT Press.

Pritchett, L., M. Woolcock, and M. Andrews. 2013. "Looking Like a State: Techniques of Persistent Failure in State Capability for Implementation." *Journal of Development Studies* 49 (1): 1–18.

Radonovich, L. J., P. D. Magalian, M. K. Hollingsworth, and G. Baracco. 2009. "Stockpiling Supplies for the Next Influenza Pandemic." *Emerging Infectious Diseases* 15 (6): e1.

Reperant, L. A., G. F. Rimmelzwaan, and A. D. M. E. Osterhaus. 2014. "Advances in Influenza Vaccination." *F1000 Prime Reports* 6: 47.

Richardson, J. S., J. D. Dekker, M. A. Croyle, and G. P. Kobinger. 2010. "Recent Advances in Ebolavirus Vaccine Development." *Human Vaccines* 6 (6): 439–49.

Roca, A., M. O. Afolabi, Y. Saidu, and B. Kampmann. 2015. "Ebola: A Holistic Approach Is Required to Achieve Effective Management and Control." *Journal of Allergy and Clinical Immunology* 135 (4): 856–67.

Rosello, A., M. Mossoko, S. Flasche, A. J. Van Hoek, P. Mbala, and others. 2015. "Ebola Virus Disease in the Democratic Republic of the Congo, 1976–2014." *eLife* 2015 (4): e09015.

Rubinson, L., R. Mutter, C. Viboud, N. Hupert, T. Uyeki, and others. 2013. "Impact of the Fall 2009 Influenza A(H1N1) pdm09 Pandemic on US Hospitals." *Medical Care* 51 (3): 259–65.

Samaan, G., M. Patel, B. Olowokure, M. C. Roces, H. Oshitani, and others. 2005. "Rumor Surveillance and Avian Influenza H5N1." *Emerging Infectious Diseases* 11 (3): 463–66.

Sands, P., A. El Turabi, P. A. Saynisch, and V. J. Dzau. 2016. "Assessment of Economic Vulnerability to Infectious Disease Crises." *The Lancet* 388 (10058): 2443–48.

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 (March): 1281–87.

Schäferhoff, M., S. Fewer, J. Kraus, E. Richter, L. H. Summers, and others. 2015. "How Much Donor Financing for Health Is Channelled to Global versus Country-Specific Aid Functions?" *The Lancet* 386 (10011): 2436–41.

Seto, W. H., D. Tsang, R. W. H. Hung, T. Y. Ching, T. K. Ng, and others. 2003. "Effectiveness of Precautions against Droplets and Contact in Prevention of Nosocomial Transmission of Severe Acute Respiratory Syndrome (SARS)." *The Lancet* 361 (9368): 1519–20.

Shuaib, F., R. Gunnala, E. O. Musa, F. J. Mahoney, O. Oguntimehin, and others. 2014. "Ebola Virus Disease Outbreak—Nigeria, July–September 2014." *Morbidity and Mortality Weekly Report (MMWR)* 63 (39): 867–72.

Simonsen, L., P. Spreeuwenberg, R. Lustig, R. J. Taylor, D. M. Fleming, and others. 2013. "Global Mortality Estimates for the 2009 Influenza Pandemic from the GLaMOR Project: A Modeling Study." *PLoS Medicine* 10 (11): e1001558.

Siu, J. Y. M. 2015. "Influence of Social Experiences in Shaping Perceptions of the Ebola Virus among African Residents of Hong Kong during the 2014 Outbreak: A Qualitative Study." *International Journal for Equity in Health* 14 (1): 88.

Smith, R. D., M. R. Keogh-Brown, T. Barnett, and J. Tait. 2009. "The Economy-Wide Impact of Pandemic Influenza on the UK: A Computable General Equilibrium Modelling Experiment." *British Medical Journal* 339 (November): b4571.

Smolinsky, M. S., M. A. Hamburg, and J. Lederberg, eds. 2003. *Microbial Threats to Health: Emergence, Detection, and Response*. Washington, DC: National Academies Press.

Stoddard, A., A. Harmer, K. Haver, G. Taylor, and P. Harvey. 2015. *The State of the Humanitarian System: 2015 Edition*. London: Active Learning Network for Accountability and Performance in Humanitarian Action/Overseas Development Institute.

Thomas, M. R., G. Smith, F. H. G. Ferreira, D. Evans, M. Maliszewska, and others. 2015. "The Economic Impact of Ebola on Sub-Saharan Africa: Updated Estimates for 2015." Working Paper 93721, World Bank, Washington, DC.

Tilman, D., and M. Clark. 2014. "Global Diets Link Environmental Sustainability and Human Health." *Nature* 515 (7528): 518–22.

Tizzoni, M., P. Bajardi, C. Poletto, J. J. Ramasco, D. Balcan, and others. 2012. "Real-Time Numerical Forecast of Global Epidemic Spreading: Case Study of 2009 A/H1N1pdm." *BMC Medicine* 10 (1): 165.

Toole, M. J., and R. J. Waldman. 1990. "Prevention of Excess Mortality in Refugee and Displaced Populations in Developing Countries." *Journal of the American Medical Association* 263 (24): 3296–302.

Twu, S-J., T-J. Chen, C-J. Chen, S. J. Olsen, L-T. Lee, and others. 2003. "Control Measures for Severe Acute Respiratory Syndrome (SARS) in Taiwan." *Emerging Infectious Diseases* 9 (6): 718–20.

Tyler, T. 2016. "IATA 2016 Annual Review." Annual review publication, International Air Transport Association (IATA), Montreal.
UNDESA (United Nations Department of Economic and Social Affairs). 2015. "World Population Prospects: The 2015 Revision, Key Findings and Advance Tables." Report ESA/P/WP.241, UNDESA, New York.
UNDP (United Nations Development Programme). 2014. "Assessing the Socio-Economic Impacts of Ebola Virus Disease in Guinea, Liberia, and Sierra Leone: The Road to Recovery." Synthesis report, UNDP, New York.
———. 2017. "A Socio-Economic Impact Assessment of the Zika Virus in Latin America and the Caribbean: With a Focus on Brazil, Colombia, and Suriname." Synthesis report, UNDP, New York.
USAID (U.S. Agency for International Development) and CDC (Centers for Disease Control and Prevention). 2016. "West Africa—Ebola Outbreak, Fact Sheet #11, Fiscal Year (FY) 2016." Fact sheet, USAID, CDC, June 24.
U.S. Department of Health and Human Services. 2005. "HHS Pandemic Influenza Plan." Strategic, guidance, and operational planning document, U.S. Department of Health and Human Services, Washington, DC.
U.S. Homeland Security Council. 2006. "Implementation Plan for the National Strategy for Pandemic Influenza." Plan document, U.S. Homeland Security Council, Executive Office of the President of the United States, Washington, DC.
Van Boeckel, T. P., S. Gandra, A. Ashok, Q. Caudron, B. T. Grenfell, and others. 2014. "Global Antibiotic Consumption 2000 to 2010: An Analysis of National Pharmaceutical Sales Data." *The Lancet Infectious Diseases* 14 (8): 742–50.
Van Boeckel, T. P., W. Thanapongtharm, T. Robinson, C. M. Biradar, X. Xiao, and others. 2012. "Improving Risk Models for Avian Influenza: The Role of Intensive Poultry Farming and Flooded Land during the 2004 Thailand Epidemic." *PLoS One* 7 (11): e49528.
Viboud, C., M. Miller, D. R. Olson, M. Osterholm, and L. Simonsen. 2010. "Preliminary Estimates of Mortality and Years of Life Lost Associated with the 2009 A/H1N1 Pandemic in the US and Comparison with Past Influenza Seasons." *PLoS Currents* 20 (March): RRN1153.
Viboud, C., L. Simonsen, R. Fuentes, J. Flores, M. A. Miller, and others. 2016. "Global Mortality Impact of the 1957–1959 Influenza Pandemic." *Journal of Infectious Diseases* 212 (11): 738–45.
Waggoner, J. J., and B. A. Pinsky. 2016. "Zika Virus: Diagnostics for an Emerging Pandemic Threat." *Journal of Clinical Microbiology* 54 (4): 860–67.
Walker, N. F., and C. J. Whitty. 2015. "Tackling Emerging Infections: Clinical and Public Health Lessons from the West African Ebola Virus Disease Outbreak." *Clinical Medicine* 15 (5): 457–60.
Wallinga, J., and P. Teunis. 2004. "Different Epidemic Curves for Severe Acute Respiratory Syndrome Reveal Similar Impacts of Control Measures." *American Journal of Epidemiology* 160 (6): 509–16.
Wang, M-D., and A. M. Jolly. 2004. "Changing Virulence of the SARS Virus: The Epidemiological Evidence." *Bulletin of the World Health Organization* 82 (7): 547–48.
Watts, J. 2004. "China Culls Wild Animals to Prevent New SARS Threat." *The Lancet* 363 (9403): 134.
WHO (World Health Organization). 1978. "Ebola Haemorrhagic Fever in Zaire, 1976. Report of an International Commission." *Bulletin of the World Health Organization* 56 (2): 271–93.
———. 2005. *International Health Regulations*. Geneva: WHO.
———. 2010. "What Is a Pandemic?" WHO, February 24. http://www.who.int/csr/disease/swineflu/frequently_asked_questions/pandemic/en/.
———. 2013a. "Global Health Workforce Shortage to Reach 12.9 Million in Coming Decades." News release, November 11.
———. 2013b. *Global Survey on National Vaccine Deployment and Vaccination Plans for Pandemic A(H1N1) 2009 Vaccine—2010*. Report of survey findings, WHO, Geneva.
———. 2013c. "IHR Core Capacity Monitoring Framework: Checklist and Indicators for Monitoring Progress in the Development of IHR Core Capacities in States Parties." International Health Regulations (2005) document, Reference WHO/HSE/GCR/2013.2, WHO, Geneva.
———. 2014. "Summary of States Parties 2013 Report on IHR Core Capacity Implementation: Regional Profiles." International Health Regulations (2005) document, Reference WHO/HSE/GCR/2014.10, WHO, Geneva.
———. 2015a. "Successful Ebola Responses in Nigeria, Senegal, and Mali." In *One Year into the Ebola Epidemic: A Deadly, Tenacious, and Unforgiving Year*. Paper Series, January 2015, WHO, Geneva.
———. 2015b. "WHO Model List of Essential Medicines, 19th ed." WHO, Geneva.
———. 2016a. *Ebola Situation Report*. Weekly data report, April 15.
———. 2016b. "Influenza (Seasonal)." Fact sheet, November. http://www.who.int/mediacentre/factsheets/fs211/en/.
———. 2016c. "Pandemic Influenza Preparedness Framework Partnership Contribution: Annual Report 2015." Document WHO/OHE/PED/2016.01, Pandemic Influenza Preparedness (PIP) Secretariat, WHO, Geneva.
———. 2017. *Situation Report: Zika Virus, Microcephaly, Guillain-Barré Syndrome*. Weekly data report, February 2.
Wolfe, N. D., P. Daszak, A. M. Kilpatrick, and D. S. Burke. 2005. "Bushmeat Hunting, Deforestation, and Prediction of Zoonotic Disease." *Emerging Infectious Diseases* 11 (12): 1822–27.
Wolfe, N. D., C. P. Dunavan, and J. Diamond. 2007. "Origins of Major Human Infectious Diseases." *Nature* 447 (7142): 279–83.
Wolicki, S. B., J. B. Nuzzo, D. L. Blazes, D. L. Pitts, J. K. Iskander, and others. 2016. "Public Health Surveillance: At the Core of the Global Health Security Agenda." *Health Security* 14 (3): 185–88.

Woolhouse, M. E. J., and S. Gowtage-Sequeria. 2005. "Host Range and Emerging and Reemerging Pathogens." *Emerging Infectious Diseases* 11 (12): 1842–47.

World Bank. 2012. *People, Pathogens, and Our Planet, Volume 2: The Economics of One Health.* Report 69145, World Bank, Washington, DC.

———. 2014. "The Economic Impact of the 2014 Ebola Epidemic: Short and Medium Term Estimates for Guinea, Liberia, and Sierra Leone." Working Paper 90748, World Bank, Washington, DC.

———. 2016. "World Bank Group Ebola Response Fact Sheet." Fact sheet, World Bank, April 6. http://www.worldbank.org/en/topic/health/brief/world-bank-group-ebola-fact-sheet.

Yamey, G., M. Schäferhoff, O. K. Aars, B. Bloom, D. Carroll, and others. 2017. "Financing of International Collective Action for Epidemic and Pandemic Preparedness." *The Lancet Global Health* 5 (8): e742–e744.

Yehualashet, Y. G., P. Mkanda, A. Gasasira, T. Erbeto, A. Onimisi, and others. 2016. "Strategic Engagement of Technical Surge Capacity for Intensified Polio Eradication Initiative in Nigeria, 2012–2015." *Journal of Infectious Diseases* 213 (Suppl 3): S116–S23.

Yu, H., J. T. Wu, B. J. Cowling, Q. Liao, V. J. Fang, and others. 2014. "Effect of Closure of Live Poultry Markets on Poultry-to-Person Transmission of Avian Influenza A H7N9 Virus: An Ecological Study." *The Lancet* 383 (9916): 541–48.

Zell, R. 2004. "Global Climate Change and the Emergence /Re-emergence of Infectious Diseases." *International Journal of Medical Microbiology Supplements* 293 (Suppl 37): 16–26.

Zinsstag, J., E. Schelling, K. Wyss, and M. B. Mahamat. 2005. "Potential of Cooperation between Human and Animal Health to Strengthen Health Systems." *The Lancet* 366 (9503): 2142–45.