

IF A GLOBAL CATASTROPHIC BIOLOGICAL RISK MATERIALIZES, AT WHAT STAGE WILL WE RECOGNIZE IT?

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GLOBAL CATASTROPHIC BIOLOGICAL RISKS (GCBRs) do not come with warning labels declaring them as such. Admittedly, if smallpox virus were released at multiple points around the world simultaneously, or if whole cities started showing major upticks in mortality from a respiratory infection, the global community would have a clear indication that a catastrophic event was occurring and would react accordingly. But there are many other scenarios—perhaps more likely in the aggregate—in which the early stages of a globally catastrophic biological event (GCBE) are much harder to identify as such (I distinguish event from risk in the sense that a risk is a possibility something will happen, and an event is when that thing actually happens). Put another way: If in the next 50 years there is a single biological event that kills 100 million people, there is a good chance the magnitude of that event will not be recognized from the start. For concreteness, this brief comment will focus on infectious diseases of humans.

Biological Uncertainty

One reason we may not immediately identify a GCBE is the inherent unpredictability of biological systems. Current understanding is that the 1918 influenza pandemic appeared in the spring/summer as a mild illness that infected many but killed few.^{1,2} After a lull in the summer, it returned in the fall in a far more lethal form. Whether this reflected a genetic change in the virus or other changes (such as increased circulation of bacteria that could cause secondary infections) remains unknown, but the fact is that with perfect information about the spring wave, public health officials would have been relatively unconcerned, yet by the fall the virus was rapidly causing arguably the greatest biological catastrophe of modern times.

Data Uncertainty

Another reason for uncertainty is our limited ability to analyze the severity or transmissibility of an infectious disease in real time.^{3,4} The 2009 H1N1 influenza pandemic, as it happened, was global but not catastrophic.⁵ Yet, public health experts remained uncertain about its severity for months after it came to light in April-May 2009. In May, data from the United States showed 1 death out of around 1,000 cases, a death rate comparable to that of seasonal influenza. Mexican data from patients who had been diagnosed with pneumonia showed 19 deaths in 504 cases, a case-fatality risk of 4%, or twice that of 1918.³

Epidemiologists noted the likely biases in directly estimating severity from these data, but they debated which biases were likely most important. Two estimates published in July gave nonoverlapping ranges for the possible case-fatality risk of 0.0004% to 0.06%⁶ and 0.2 to 1.2%.⁷ Not until the late summer or early fall were there enough high-quality data to make a confident estimate that the true risk of dying was 0.09% or less.⁸ Even then, the range of estimates spanned an order of magnitude, but for practical purposes it was clear that overall severity was in the range typical of seasonal influenza. Importantly, for younger age groups it was considerably more severe than the near-zero mortality risk they faced from typical seasonal influenza, but it was not catastrophic.

Similarly, early estimates of the transmissibility of the infection in the United States suffered from uncertainty due to incomplete data: Various assumptions about how reporting rates were changing over the course of the early spread could give reassuring estimates that the virus was spreading relatively slowly or more concerning ones that it was spreading fast enough that control would be impossible without a highly effective vaccine.⁹

The Role of History

When events, such as new infectious diseases, occur that may become globally catastrophic, history can be an invaluable guide. Global biological catastrophes have fortunately been rare in history, so historical examples are few. However, historical examples can provide “existence proofs” that a particular course of events can happen. Patterns of spread in different US cities with different levels of control measures showed that non-pharmaceutical interventions could retard the spread of 1918 influenza,^{10,11} and this historical example has been appropriately used in pandemic planning for future severe pandemics.¹²

The 1918 and 1957 influenza pandemics showed peak activity not in the normal flu season (winter) but earlier, in the mid- to late autumn.² These historical examples—along with mathematical modeling results—could have been used for planning of vaccine supplies in 2009,¹³ but awareness of them seems to have been limited at the time. Likewise, the increased virulence of the 1918 influenza in the fall compared to the milder spring might have been taken as a legitimate justification for aggressive action to secure vaccines and antivirals in 2009, even if the relatively mild course of illness in spring 2009 had been confidently documented. After all, in 1 of 3 historic pandemics of the 20th century, a mild spring wave had been followed by a catastrophic autumn wave, so planners might legitimately have considered that a reasonable scenario to plan for.

There is an important asymmetry in how we evaluate risk based on historical examples. If a sequence of events has happened in the past, we are well justified in considering it a possible or likely scenario in future events, as in the examples in the preceding paragraph. If a particular course of events has *not* happened in the recorded past, we should be far more cautious about concluding it will not happen in the future. As an example: If asked in 2013 whether an outbreak of Ebola virus disease could get out of control and infect more than 10,000 people, many observers, including me, would likely have said it was not much of a risk. From the virus’s discovery in 1976 to mid-2013, there had been 26 separate instances in which at least 1 person had known, symptomatic Ebola virus infection, most of them in sub-Saharan Africa (<https://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html>). The outbreaks that resulted ranged in size from 1 person (the index case) to 425. Based on this history, many of us would have said that basic public health measures can contain an Ebola outbreak before it spreads widely.

Such reasoning—proven wrong by the estimated 28,652 cases in the 2014-15 outbreak in Guinea, Sierra Leone, and Liberia—would have missed 2 key points. First, circumstances differ, and, in particular, controlling an outbreak with public health measures means detecting and identifying it while it is still small. Failures of sur-

veillance and response can (and did) allow the epidemic to reach a size where containment becomes far more difficult. Second, the fact that public health had succeeded in controlling 26 Ebola outbreaks was not evidence that it would do so every time. The so-called rule of 3 in medical decision making is that if an event has occurred zero times out of X times when it might have occurred, we can be relatively confident that the probability of its occurring was less than 3/X.¹⁴ In the case of Ebola outbreaks, an uncontrolled outbreak had occurred in zero of the 26 events prior to 2014, so (under the assumption that the probability of losing control was the same in each of those outbreaks) we should have been confident that the probability of losing control of an Ebola outbreak was less than about 12%, or 3/26. To use a common analogy: If we have a big urn full of black and red balls, and we draw a black ball 26 times in a row, we can’t be sure of how many of the balls in the urn are red. Basic probability theory says that the 95% confidence interval for the proportion of red balls in the urn runs from about 0 to 12%. Operationally, these are very different numbers! Yet, we are not good at thinking rationally about unusual events,¹⁵⁻¹⁸ and incentives sometimes exist to act as if they were less common than they are.¹⁹ We should beware of “it’s never happened before” as a guide to planning for the future.

Practical Implications

These considerations have concrete implications for the effort to identify, reduce the probability and impact of, and respond to GCBR.

1. Preparing for GCBR means preparing for smaller-impact risks to ensure that they do not become globally catastrophic. Effective control of an outbreak while it is small is the most effective way to ensure that the more difficult effort to control a widespread outbreak never becomes necessary. Biologically, the amount of genetic variation in a pathogen population rises as the number of infected people grows, thereby increasing the risk of pathogen evolution to greater severity or contagiousness, or to acquiring a new route of transmission. Keeping small outbreaks from growing is an essential part of GCBR preparedness. Another consideration reinforcing this approach is the human element: Systems that are designed to be used only for global catastrophes will, we can hope, often go unused for decades or more. Such systems are unlikely to be kept in working order and continuously improved unless they find application in responding to more common, subcatastrophic events.
2. Improving systems and methods to gather, process, interpret, and share information for outbreaks fast

and accurately will speed the resolution of data uncertainty, so that resources can be more knowledgeably allocated to counter the most threatening risks. These include but are not limited to enhancing global surveillance for illness in humans and animals, building systems for rapid sharing of data and interpretations of data that can be used by decision makers, and methodological work to improve the quality and quantity of data available and to improve its interpretation.

3. Efforts to predict the nature of GCBR, and even to create ordered lists of potential ones, are essential; our preparedness will be best for those threats we have already considered and understood, as has been done in the past for deliberate biological threats.²⁰
4. At the same time, efforts to prepare for such risks should constantly emphasize the value of countermeasures that can be effective even if predictions are wrong—if we have a globally catastrophic outbreak of an unknown pathogen, or (as in all influenza pandemics to date) we fail to detect the ancestors of the pandemic virus and know there is a pandemic only after it is under way.²¹ This means that prediction-reliant investments—development and stockpiling of vaccines against known threats, culling of animals infected with viruses judged to be high risk—should be balanced by investments that could pay dividends under many scenarios, predictable or not.²² These include the development of universal influenza vaccines (which may protect against any new pandemic strain), investments in public health infrastructure and health systems to facilitate rapid response to any outbreak, development of vaccine platforms and technologies to speed development of vaccines to unknown pathogens, and improvements in information systems, data-sharing platforms, and methods for interpreting data in outbreaks.

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