The Next BIG ONE

THE PUBLIC HEALTH COMPANY

What will the next ‘big one’ look like?

Outbreaks are becoming more severe and frequent. We outline four primary risk factors that shed light on what the next pandemic could be.

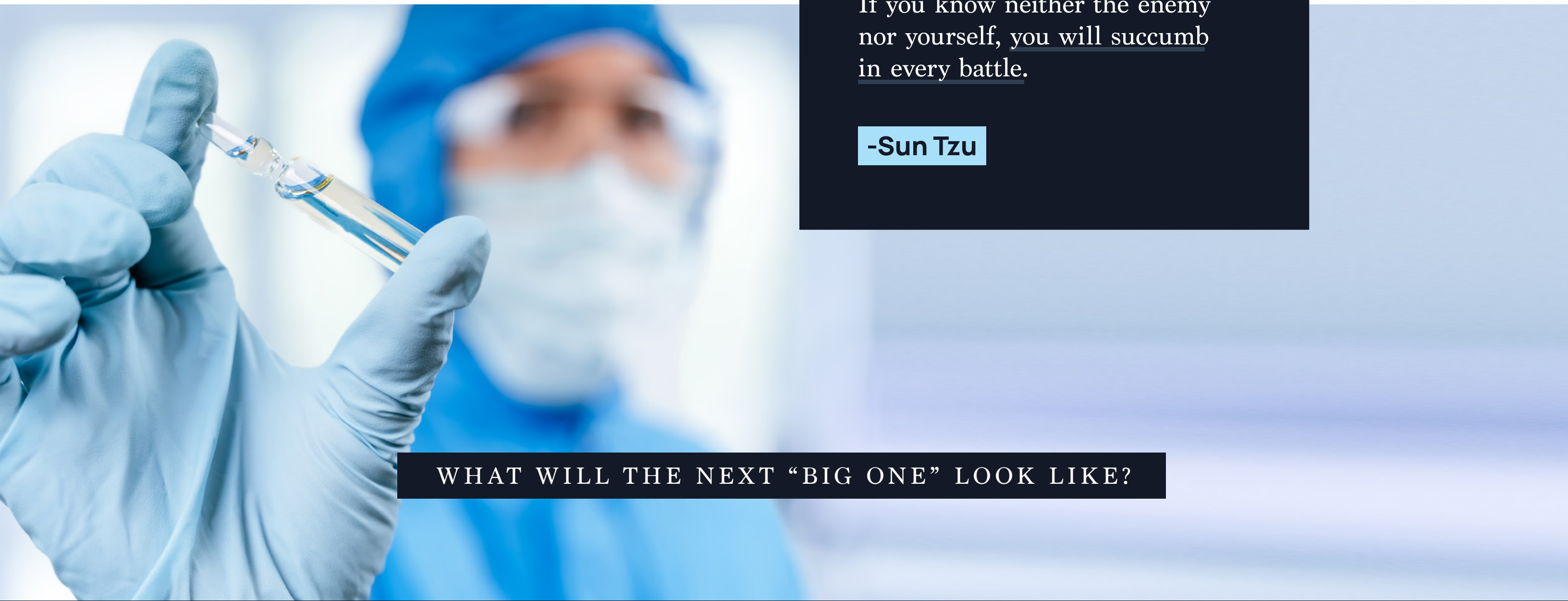
Infectious disease epidemics have endured throughout human history. From smallpox infecting pharaohs in ancient Egypt, the plague killing a third of the population in Europe during the Middle Ages, the devastating 1918 influenza pandemic claiming more individuals globally than the contemporaneous World War I, to the present-day COVID-19 pandemic rapidly sweeping across the world, the impact and prevailing presence of infectious disease spread is irrefutable.

Although the world has many more tools to combat infectious diseases now, a small local outbreak can quickly turn into a global pandemic due to global connectedness, increasingly dense population centers due to urbanization, and an ever-growing human population. Whereas smallpox took many centuries to spread across all corners of the world, it took less than three months for COVID-19 to spread to every continent (excluding Antarctica).

As the vaccine rollout continues across the U.S. and the light at the end of the tunnel becomes ever closer, many are taking the time to reflect on the past year before interest in infectious diseases diminishes. Lessons learnt from coping with the tragic missteps of 2020 can strengthen our defense against future biothreats.

The next pandemic is not a matter of if, but when and what. The 'when' is difficult to predict given the randomness of infectious disease emergence, however there is data to suggest what the next pathogen might be. The world will be much better prepared to take on the next 'big one' if the pathogen can be predicted. In this white paper, we will discuss the likely causes of a global epidemic, i.e., a pandemic, but also other pathogens that can cause deadly epidemics on a smaller geographic scale.

> "
>
> If you know the enemy and know yourself, you need not fear the result of a hundred battles.
>
> If you know yourself but not the enemy, for every victory gained you will also suffer a defeat.
>
> If you know neither the enemy nor yourself, you will succumb in every battle.
>
> **-Sun Tzu**



WHAT WILL THE NEXT "BIG ONE" LOOK LIKE?

THE PUBLIC HEALTH COMPANY

Four risk factors for a pandemic:

All pathogens can cause outbreaks, though their magnitude and severity will vary depending on factors such as attributes of the pathogen itself, human population, and environment. Below are the four key factors that determine how big and how deadly an infectious disease outbreak can become:

1. **Contact rate:** the rate of an infected individual making contact with other people where a transmission is possible
2. **Transmission risk:** probability of a transmission per contact
3. **Case-ascertainment rate (CAR):** the proportion of infected individuals who are confirmed as infected
4. **Case-fatality rate (CFR):** the proportion of individuals who die after being infected

Most of these factors are affected by the route of transmission (see Table and Figure 1). Grouping infectious diseases accordingly, we will explore the potential outcome of each pathogen type, examples of impact on different industries, and highlight current systematic vulnerabilities to improve future preparedness.

The relative outbreak risks of different types of infectious diseases

TABLE 1

Example Pathogen	Transmission Route	Contact Rate	Transmission Risk	CAR	CFR	Potential Outbreak Size
COVID-19	Airborne	High Risk	Medium Risk	High Risk	Low Risk	Worldwide
Dengue	Vector	Medium Risk	Medium Risk	High Risk	Low Risk	Continent
Ebola	Direct	Medium Risk	High Risk	Low Risk	High Risk	Continent
MRSA	Fomite	High Risk	Medium Risk	Medium Risk	High Risk	Continent
E coli O157:H7	Ingestion	Low Risk	Medium Risk	Medium Risk	Medium Risk	County/State
Anthrax	Released	Low Risk	High Risk	Low Risk	High Risk	County/State

Low Risk | Medium Risk | High Risk

Diseases that are highly contagious tend to be less deadly, and vice-versa

FIGURE 1

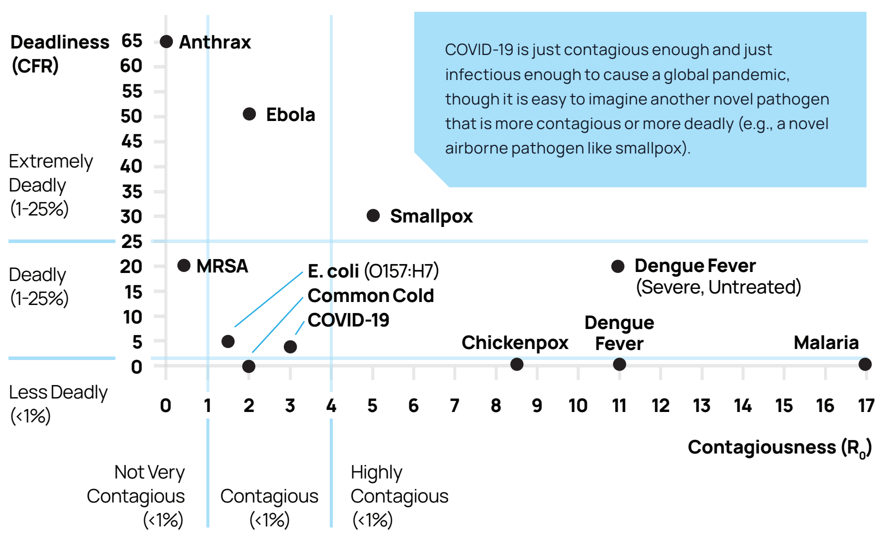


Figure legend:
R_0 is the basic reproduction number, which indicates how many new infections result from a single case.
The case fatality rate (CFR) is the % of people who die as a result of contracting the disease.

1 Airborne

The largest disease outbreaks in the last two centuries have been caused by influenza viruses and coronaviruses, which both spread primarily through droplet and aerosol (micro droplets that can linger in the air) transmission. For simplicity, both types of transmission are classified as airborne here.

There are several reasons airborne respiratory pathogens are the most likely culprits of global pandemics. Although infections caused by these pathogens tend to be short, aerosol and droplet transmission[1] score the highest in terms of contact rate, which is exacerbated in densely populated urban settings.

It's not just the high contact rate that contributes to the pandemic potential of airborne pathogens; there often exists an evolutionary counterbalance between transmissibility and CFR. COVID-19 was sufficiently transmissible to rapidly spread across the world and had a high enough CFR to overcrowd hospitals with the seriously ill. Furthermore, the pre-symptomatic transmission of COVID-19 makes it difficult to control the spread without using strict quarantine measures.

Pre-symptomatic and asymptomatic transmission led to all industries being impacted by the COVID-19 pandemic as shutdowns were the most effective tools to curtail the spread in the absence of mass ongoing asymptomatic testing. This pre-symptomatic and asymptomatic transmission also enabled COVID-19 to spread across the globe quickly, with very low case-ascertainment rates.

Thinking ahead, rapid reporting of emerging pathogens with high reproductive rates, widespread deployment of point-of-care testing, swift quarantining measures, and quick determination of the role asymptomatic persons play in transmission will improve the rapid containment of an emerging airborne pathogen.

The combination of high contact rate, increasing human population density, and increasing global connectedness make airborne pathogens the most likely candidate to cause the next pandemic.

2 Vector-borne

Climate change is leading to the invasion of *Aedes aegypti* mosquitoes more broadly across the U.S.[2] These mosquitoes carry some of the deadliest pathogens and have caused large epidemics across the world: Zika, dengue, yellow fever, chikungunya, and more. Most recently, the large Zika epidemic spread to southern U.S. states such as Florida. The Aedes mosquitoes have been identified in 22 California counties in recent years, their migration attributed to global warming trends.[3,4] This raises the concern of yellow fever and dengue spiking again in the U.S.

The best interventions for mosquito-borne diseases are vector control and vaccination. Mosquito abatement districts across the U.S. work to reduce mosquito populations through targeted spraying of mosquito repellants and removing mosquito reservoirs. However, mosquitos are developing resistance to repellants, making them harder to control. Vaccines are available for some vector-borne diseases (yellow fever) while others are advancing (malaria, dengue).

The tourism and business links between the U.S. and other countries in the Americas make it likely that an epidemic will land on U.S. shores via seaports and airports. Those cities, as well as the transportation industry, would thus be at the frontline of such an epidemic on U.S. soil.

As with the COVID-19 pandemic, a mosquito-borne epidemic in the U.S. would also exacerbate socioeconomic inequities. Those with air conditioning, screens in the homes, access to personal mosquito repellants, and ability to work indoors would be much better protected against such an epidemic. Improvements in infrastructure can help alleviate some of the inequities, for example by stockpiling mosquito repellants for distribution to the general population during an emergency.

While a repeat of the infamous Black Death (caused by bubonic plague, or the bacterium Yersinia pestis spread through fleas) is unlikely in modern times due to better rodent control. However, pathogens spread by mosquitoes and other arthropods (e.g., insects and arachnids) could impact a larger portion of the population as the effects of climate change advance. Vector-borne epidemics across southern states in the U.S. and across the Americas will no doubt occur with increasing regularity as the range of suitable habitats for these insect vectors continues to expand.

3 Direct

Compared to airborne and vector-borne pathogens, directly transmitted pathogens tend to be more deadly. These are diseases transmitted through direct contact with infected bodily fluids or blood, for example touching, kissing, or sexual contact. One of the most well-known directly transmitted pathogens is Ebola, which has caused epidemics in West Africa over the last decade. Because Ebola does not cause pre-symptomatic transmissions, and most people do show symptoms, it is unlikely to cause as big of an outbreak as airborne or vector-borne pathogens, but induces more fear given the high CFR of 50%.[5]

Given the rarity of Ebola in the U.S. there is a very real risk that early Ebola cases would go unrecognized by healthcare providers who would in turn handle infectious patients without adequate personal protective equipment (PPE). Undetected community spread of the disease is made increasingly possible in the U.S. with the potential introduction of strains that display a pre-symptomatic spread component.

Healthcare workers are at especially high risk of Ebola exposure as patients are most infectious when they start showing symptoms. PPE is thus even more crucial when treating an Ebola suspect than a COVID-19 suspect; a shortage of PPE in the face of community-spread Ebola would be devastating to the healthcare workforce.

With directly transmitted diseases, fast-growing pandemics are less likely because much closer contact is required for transmission than airborne diseases. However, localized outbreaks across a country or a continent are possible, as seen in Ebola, and still have devastating impacts to local economies and lives.

4 Fomite

While contaminated surfaces proved to be only a small contributor to COVID-19 transmission,[6] it is a major driver in many bacterial and fungal infections. Healthcare settings are particularly prone to fomite transmissions due to the density of people (patients, healthcare professionals, and visitors), more infectious patients than in the general population, and necessary reuse of equipment and rooms. The greater number of immunocompromised patients in a healthcare setting compared to the general population also leads to worse outcomes for these individuals.

Outbreaks due to fomite transmission are unlikely to be large in the U.S. general population because of access to clean water and cleaning agents. However, deadly outbreaks can still occur if the bacterial or fungal pathogens carry antimicrobial resistance. Antibiotic-resistant infections (like carbapenem-resistant Enterobacterales) are linked to 35,000 U.S. deaths annually, many of them from fomite transmission.

Clostridioides difficile (C. diff) in particular highlights the difficulties faced by hospital infection control programs. This bacterium is responsible for half a million infections in the U.S. each year, causing severe diarrhea among those who are infected, and has a high CFR of 11%.[7] Antibiotics are a key component of prevention of and response to infections in healthcare settings, yet increasing antibiotic use is associated with increases in *C. diff*.[8] The COVID-19 pandemic has exacerbated this antibiotic-resistance problem with increased antibiotic use due to COVID-19 hospitalizations.[9]

The best tools against such infections are improved prevention measures in healthcare settings and limited antibiotic resistance through data-driven antibiotic stewardship practices. Sophisticated immunotherapies and phage-based therapies are promising tools for combating antibiotic-resistant infections. Data science tools to find and link potential carriers of these organisms, such as genomic epidemiology, can rapidly contain outbreaks and identify genomic markers of antibiotic resistance spreading in a community.

Because fomite transmission requires a source of infection, they tend to be limited to small outbreaks localized in a single geographic region. Though contact rate and transmission risk may be high for the location, targeted cleaning measures are often sufficient to contain the spread.

5 Ingestion

Public health measures to improve food safety and water sanitation over the last century have reduced the prevalence of diseases caused by food and water contamination.[10] However, the increasing reliance on antibiotics in agriculture has resulted in more antibiotic-resistant bacteria, which end up in meat as well as in soil and water, leading to contaminated fruits and vegetables.[11]

If these products are consumed across the country, then the outbreak can become both very large and deadly as observed with repeated E. coli[12] and Salmonella[13] outbreaks. As recently as February 2021, when the U.S. was still in pandemic lockdown, an E. coli outbreak caused by the particularly virulent strain O157:H7 spread across 5 states and killed at least one individual.[13]

Food-born illnesses also have economic consequences. In another E. coli outbreak, contaminated flour led to the recall of not only flour products, but also downstream products such as cookie mixes.[16] The food industry endures the brunt of such outbreaks because of economic consequences, impact on consumer trust, and government penalties from food recalls. [14,15]

Rapid detection of food-borne illnesses (e.g., by using genomics to link infections across wide geographic regions) and robust adherence to optimal manufacturing/food processing practices and antibiotic stewardship for agriculture are important steps in mitigating the risks of continued large food-borne outbreaks in the U.S. Genomic epidemiology is also an important tool for rapidly identifying outbreaks and identifying sources of outbreaks when relevant metadata are available.

Like fomite transmission, pathogens transmitted through ingestion require a source, so they tend to cause small outbreaks. Though these outbreaks may be small compared to epidemics caused by airborne and vector borne diseases, they can be geographically widespread as contaminated produce can travel large distances, potentially internationally.

6 Accidental or intentional release

While this is the least likely scenario for a large outbreak, it is potentially the deadliest. In the case of engineered pathogens, there are gain-of-function experiments done on pathogenic viruses to better understand their viral genes. However, human error or an environmental disaster can occur, accidentally releasing such agents into the population and leading to potentially deadly outbreaks.[17]

Similarly, bioterrorism attacks often make use of highly deadly pathogens such as anthrax, plague, or pathogens with low immunity among the human population such as smallpox. The COVID-19 pandemic exposed the weaknesses in U.S. biothreat defense, increasing the threat of bioterrorism relative to pre-pandemic levels.

Improving preparedness against these outbreaks requires a robust surveillance system of suspicious infections, rapid identification methods for identifying the pathogen, quick investigations or algorithms to identify sources of infections, simultaneous coordination of investigations happening in different regions, rapid containment strategies and interventions, and a clear communication plan for the public to minimize fear and instill trust.

The released pathogens will probably have a high CFR and therefore low transmissibility. However, the most concerning scenario would be the inadvertent or intentional release of highly transmissible pathogens that also have sufficiently high CFR to cause hospital systems to be overwhelmed, e.g., smallpox or laboratory strains of influenza.

Concluding remarks

Although it is difficult to predict when the next 'big one' will happen, it will likely be similar to something we have seen before. The pandemics of the last century have all been caused by influenza. The COVID-19 pandemic was caused by a pathogen related to a seasonal coronavirus that causes colds and the SARS epidemic in 2003. Thus, the next pandemic will likely be caused by another airborne pathogen, probably in the influenza and coronavirus families, with a period of pre-symptomatic transmission able to disseminate quickly and widely due to global air travel and crowding.

However, a global pandemic is not the only biothreat the U.S. should prepare for. Epidemics that spread across parts of the country or across a single continent can still have grave repercussions for healthcare systems and economies. Dengue, Zika, and Ebola epidemics have increased in frequency in recent years despite being caused by pathogens that have been known for many decades, and they will likely return to U.S. shores once global travel resumes. Furthermore, pathogens (whether released intentionally or accidentally) present a less likely but far more catastrophic biosecurity risk that could cause large outbreaks in the U.S. due to extremely high case fatality or transmission rates.

While fortifying healthcare and technology infrastructure is needed for pandemic preparedness, we also need to safeguard the parts of the system that have protected us over the last year: public health officers, epidemiologists, public health nurses, doctors, nurses, scientists, janitorial staff, and delivery services.

There are hundreds of pathogens that could cause outbreaks in the U.S. spread through any of the transmission routes described in this white paper. Improving infrastructure to better prevent, detect, and contain these smaller but more frequent threats will help us prepare for the next 'big one.' These improvements are further detailed in another white paper, 'The Future of U.S. Public Health.'

References

1. Morawska, L. & Milton, D. K. It Is Time to Address Airborne Transmission of Coronavirus Disease 2019 (COVID-19). Clin. Infect. Dis. ciaa939 (2020) doi:10.1093/cid/ciaa939.

2. Iwamura, T., Guzman-Holst, A. & Murray, K. A. Accelerating invasion potential of disease vector Aedes aegypti under climate change. Nat. Commun. 11, 2130 (2020).

3. California Department of Public Health. Aedes aegypti and Aedes albopictus Mosquitoes in California by County/City. https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/AedesDistributionMap.pdf (2021).

4. California Department of Public Health. Aedes aegypti and Aedes albopictus mosquitoes. https://www.cdph.ca.gov/Programs/CID/DCDC/pages/Aedes-aegypti-and-Aedes-albopictus-mosquitoes.aspx (2021).

5. World Health Organization. Ebola virus disease. https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease (2021).

6. Fennelly, K. P. Particle sizes of infectious aerosols: implications for infection control. Lancet Respir. Med. 8, 914–924 (2020).

7. CDC. What is C. diff? https://www.cdc.gov/cdiff/what-is.html.

8. Ferreira, E. de O., Penna, B. & Yates, E. A. Should We Be Worried About Clostridioides difficile During the SARS-CoV2 Pandemic? Front. Microbiol. 11, 581343 (2020).

9. Bengoechea, J. A. & Bamford, C. G. SARS-CoV-2, bacterial co-infections, and AMR: the deadly trio in COVID-19? EMBO Mol. Med. 12, (2020).

10. CDC. Achievements in Public Health, 1900-1999: Safer and Healthier Foods. MMWR 48, 905–913 (1999).

11. Thanner, S., Drissner, D. & Walsh, F. Antimicrobial Resistance in Agriculture. mBio 7, e02227-15, /mbio/7/2/e02227-15.atom (2016).

12. Rangel, J. M., Sparling, P. H., Crowe, C., Griffin, P. M. & Swerdlow, D. L. Epidemiology of Escherichia coli O157:H7 Outbreaks, United States, 1982–2002. Emerg. Infect. Dis. 11, 603–609 (2005).

13. CDC. CDC investigating multistate E. coli outbreak with unknown food source. https://www.cdc.gov/media/releases/2021/s0203-e-coli-outbreak.html#:~:text=CDC%20and%20state%20and%20federal,%2C%20and%20Washington%20(2). (2021).

14. Dennis, E. J., Ajewole, K., Bergtold, J. S. & Schroeder, T. C. Consumer Reactions to E. Coli and Antibiotic Residue Recalls: Utility Maximization vs. Regret Minimization. Front. Vet. Sci. 7, 611 (2020).

15. SmartSense. The True Costs of Food Recalls. https://blog.smartsense.co/costs-of-food-recalls (2019).

16. CDC. Outbreak of E. coli Infections Linked to Flour. https://www.cdc.gov/ecoli/2019/flour-05-19/index.html#:~:text=coli)%20O26%20infections%20linked%20to%20flour.&text=On%20June%2021%2C%202019%2C%20Brand,coli. (2019).

17. Lipsitch, M. Why Do Exceptionally Dangerous Gain-of-Function Experiments in Influenza? in Influenza Virus (ed. Yamauchi, Y.) vol. 1836 589–608 (Springer New York, 2018).