Preventing the next pandemic

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HIGHLIGHTS

- Preventing the next pandemic is critical for protecting human lives, reducing public health costs, and easing financial impacts.
- Surveillance and early detection of microbes with high pandemic potential combined with transparent and timely data sharing are paramount to identifying novel pathogens and limiting injurious spread.
- Public health measures implemented before, during, and after a new pandemic can slow the spread of illness; continued advancements in science and technology curb widespread disease.

Scientists have increasingly sounded the alarm about insufficient global pandemic preparedness, messaging which has appropriately escalated in the past two decades after the SARS (Severe acute respiratory syndrome), MERS (Middle East respiratory syndrome), and Ebola outbreaks [1]. This global lack of readiness was revealed during the most recent COVID-19 pandemic via slow threat recognition, early mixed public health messaging, supply chain disruptions, and vaccine rollout challenges [2]. This article reviews how pandemic pathogens originate and describes methods of early pathogen detection. It also details how multi-level interventions such as public health messaging, widespread accessible testing, and international cooperation, including funding, are critical tools for mitigating the spread of disease. Finally, we discuss how advancements in biotechnology help counter widespread outbreaks, including the use of early molecular diagnostics, application of therapeutics, and the development of "plug and play" vaccines. The world demands early and strong preparation to prevent the next pandemic.

Introduction

"A GAUZE MASK IS 99% PROOF AGAINST INFLUENZA. Doctors wear them. Those who do not wear them get sick. The man or woman or child who will not wear a mask is now a dangerous slacker."

-San Francisco Chronicle, October 22, 1918

At the onset of the 1918 United States (U.S.) influenza outbreak at an Army barracks in Kansas, scientists worked feverishly to identify modes of transmission to limit spread in the troops' overcrowded quarters. In the midst of World War I, the Army's manpower was needed elsewhere. W. H. Kellogg, scientist and physician, quickly discovered that multiple layers of gauze prevented dangerous droplet transmission of this newly-described respiratory illness [3]. In brisk response, government officials, scientists, and public health officers called on all citizens to don masks. Some citizens voiced distrust and unwillingness to comply with this recommendation, a sentiment recognized still a century later [4]. Additional clear and simple public health messages: open windows, stay away from the sick, stay home, and do not crowd, sound remarkably familiar today (Fig. 1). While pandemics are not a new phenomenon, the COVID-19 pandemic has laid bare the global lack of preparation for such a threat. In this article we will:

- Introduce the origin of pandemics and candidate pathogens for the next pandemic
- Consider the benefits of zoonotic screening and surveillance for early pandemic detection
- Review specific advances in biotechnology that allow for better preparedness

How do pandemics arise?

The distinction between pandemics, infections spread over vast geographies, and epidemics, infections more limited in their geographic scope, is suggested by the Greek origin of the name, *pan demos* or "all people" [5]. Widespread infectious disease arose when humans developed agriculture, resulting in dense human settlements. Closely knit populations of humans and livestock provided favorable conditions to sustain the transmission of infectious diseases [6]. In these agrarian societies, natural barriers like bodies of water and mountains along with the speed of human travel, e.g. the footspeed of merchants navigating the Silk Road, limited the distance a disease could spread [7]. Today, widely interconnected

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Figure 1: Public health messaging in the United States during the 1918 influenza pandemic. Chicago Department of Health.

global populations allow infectious diseases to be boundless international threats. As global physical barriers subside, the biological nature of a pathogen is now the primary determinant of its potential to cause a pandemic.

Pathogens are microorganisms that cause disease. Human pathogens consist of diverse biological agents: bacteria, viruses, protozoa, fungi, etc., yet few of these pathogens harbor the high-risk features required to cause a pandemic (Fig. 2). Throughout history, pandemics have been almost exclusively caused by bacteria and viruses due to their high transmissibility and fast rate of spread [8]. Improvements in community sanitation and the advent of antibiotics in the 20th century mitigated the threat of bacterial pandemics. The bacterium *Yersinia pestis*, which causes bubonic plague, remained a pandemic-level threat since it arose as a pathogen approximately 4000 years ago [9]. With the advent of antibiotics and improved public sanitation, its mortality rate fell from 70% to 10% [9]–[11]. Due to robust measures to prevent and treat bacterial infections, viruses currently surpass bacteria as pathogens with the greatest pandemic potential. Viral pathogens of pandemic potential are increasing and a number of features contribute: fast replication, airborne and droplet transmissibility, poor treatment options, and propensity for pre-symptomatic or asymptomatic spread [12]. Of viruses, RNA viruses are more likely to cause a pandemic than DNA viruses. This is primarily due to their high genetic mutation rate, which in turn increases the potential of RNA viruses to spread more easily among humans and animals and to escape antiviral therapies [13]–[15]. While viruses are currently the most likely pathogens to cause a pandemic in humans, all contemporary pathogens benefit from the potential of unhampered spread via limited geographic barriers.

Pandemic pathogens primarily arise as zoonoses,

or diseases transmitted from animals to humans [17]. Approximately 40–95% of infectious diseases are zoonotic in origin, a rate which varies by the type of microorganism [23]. An estimated 72% of zoonotic diseases arise from a wildlife source [24]. Livestock are also essential to the spread of zoonotic disease, and diseases will often transmit within the human-livestock-wildlife interface [25]. For example, genetic sequencing data from each pandemic influenza virus of the 20th century revealed high genetic similarity to known swine and avian influenza viruses, tracing the origins of these pandemics to multiple animal hosts [26, 27].

Three ecological stages describe the emergence of a pathogen into a pandemic of zoonotic origin (Fig. 3) [17]. During stage one, the pathogen replicates and cycles between animal hosts, which act as natural reservoirs. At this stage it has not yet caused human disease, but a pathogen can spread to other non-human hosts, a new geographic region, or begin to multiply beyond its reservoir. In order to progress to stage two, the pathogen must be able to infect humans. This typically occurs via the acquisition of random genetic mutations, however this is not universally true. For example, urbanization and human encroachment on wildlife habitats can introduce novel pathogens to society which may already be able to infect humans without acquiring new mutations [25]. Finally in stage three, sustained transmission and spread between humans across the globe occurs, introducing the pathogen to uninfected populations. When the pathogen reaches stage three, it causes a pandemic.

Committed and relentless study of the features of high-risk pandemic pathogens (transmissibility, mutability) at the early stages of zoonotic disease and the ecological conditions facilitating the transition from an animal pathogen to a human pandemic could serve as a valuable early warning system. Such efforts were highly recommended in the wake of the

	RNA Viruses	DNA Viruses	Bacteria	Fungi	Protozoa ^a (Parasites)
Pandemic Potential	High	Moderate	Moderate, historically high	Low	Low
Features	Continual threat due to RNA genomes prone to mutation; fast viral reproduction and transmission; propensity to cause respiratory infections with airborne potential	Less prone to mutations than RNA viruses and transmission less likely to be airborne	Slower reproduction than viruses, less mutation prone, but able to transfer fitness genes; Threat now reduced due to fast detection and well-developed treatments	Nontraditional pandemic threat due to slow speed of spread and effective antifungals, though multidrug resistant organisms are increasing	Pandemic threat is low due to spread through vector, however malaria is estimated to contribute to half of all human deaths throughout history
Speed of Transmission	Fast	Fast-Medium	Medium	Slow	Slow-Medium
Mode of Transmission	Airborne Respiratory, Droplet, contact with infected fluids	Droplet, contact with infected fluids or materials (fabric)	Droplet (respiratory); Contact with infected humans or animals	Airborne spores; Contact with infected humans or animals; Environmental	Generally through an intermediate host (vector)
Detection Methods	PCR-based (hours) Select Antigens (hours-days)	PCR-based (hours) Antibodies (hours-days)	Bacterial culture (days), PCR-based (hours)	Fungal culture (days) Select antigen tests	Microscopy (hours) PCR-based (hours)
Countermeasures	Masks for respiratory transmission, antivirals, vaccines if available	Vaccines, standard precautions ^b	Vaccines, antibiotics, improved sanitation	Antifungals, control of environmental fungal threats	Barriers between hosts and humans, elimination of reservoirs, anti-parasitic medications
Examples of Pandemic Pathogens	SARS-CoV1 (SARS) SARS-CoV2 (COVID-19) Ebola (Hemorrhagic Fever) HIV (AIDS) Influenza (Spanish, Swine, Avian flus)	<i>Variola major</i> (Smallpox)	<i>Yersinia pestis</i> (Bubonic Plague) <i>Vibrio cholera</i> (cholera) <i>Mycobacterium tuberculosis</i> (TB)	No human pandemics caused by fungi; widespread fungal disease affecting bats, frogs; fungi posited to contribute to dinosaur die-off	<i>Plasmodium spp</i> (malaria) <i>Trypanosoma lewisi</i> (widespread death of the Christmas Island Rat)

Figure 2: Characteristics of microorganisms as pandemic threats. ^aSingle-celled organisms of which parasites may be one type. ^bStandard (formerly universal) precautions include hand and respiratory hygiene, use of personal protective equipment, sterile and aseptic techniques, etc. [16]. Images created with BioRender.com. Table adapted from references [8, 12]–[22].

2003 SARS outbreak, which was caused by a coronavirus with the potential of turning into a pandemic [28]. The outbreak was not contained due to early detection but rather due to the biological nature of the pathogen along with strict and effective public health measures [29]. Scientists globally argued for early surveillance and screening, discussed further below, but these efforts ultimately lost momentum. Post-SARS remains a clear example as to how relaxation of the scientific study of pathogens of pandemic potential yields lack of preparation for the next.

How do we detect emerging and reemerging pathogens?

Frequent surveillance remains the cornerstone to detecting pathogens circulating in and between animal hosts, reflecting disease risk to animals, disease risk to humans, and the possibility of an emerging pandemic. Numerous viruses of pandemic potential have wildlife origins, and pathogens have been increasingly crossing the xenographic, or species barrier, in the last decade. Serious new infections commonly arise from bats (Ebola, Marburg, SARS, COVID-19, Nipah virus), though infectious origins in primates (HIV, Zika) and other mammals (SARS via palm civets) are also common. Influenza has permanent animal reservoirs in waterfowl, poultry, and swine [30, 31]. Bidirectional mixing of viral genomes was spotlighted in the 2009 influenza H1N1 pandemic with more virulent mutations acquired as the flu was shared back and forth between humans and pigs [30, 31].

Numerous domestic and international groups are advocating for preemptive disease surveillance in animals

dwelling near humans, specifically high-risk wildlife and animals of the food supply chain. The U.S. Agency for International Development (USAID) is one champion for global pathogen surveillance as a measure of future pandemic prevention. Project PREDICT under USAID is one group carrying the torch of worldwide pathogen surveillance in animals and, to date, has screened 164 000 organisms in humans and animals in 30+ countries, uncovering 947 novel viruses and 217 known viruses of pandemic potential [32]. A counterpart program performing screening (frequent testing of healthy animals and humans) and surveillance (specific testing for pathogens) in the U.S. includes the National Syndromic Surveillance Program (NSSP). Born out of growing concern for detecting bioterrorism, the NSSP serves as an early warning beacon for diseases of public health concern by sharing hospital emergency departments' data nationally [33]. Surveillance at multiple levels—wildlife, livestock, veterinary clinics, emergency rooms, public health departments—paired with global data sharing, could be supported and potentially incentivized to prevent future pandemics. Coordinated data sharing at the global level may help speed the time from novel pathogen detection to recognition of its potential as a disease-causing pandemic pathogen to public health response.

Evidence of success lies both with SARS and COVID-19, where early data sharing of clusters of disease and viral genome sequences allowed rapid test development, global implementation of local surveillance,

Figure 3: Pathogens can be described as progressing through three stages to becoming a pandemic, outlined by Morse and colleagues [17]. Stage one: the pathogen is circulating and replicating in a non-human organism or environment, also known as a reservoir. Stage two: the pathogen acquires mutations that facilitate its spread from livestock or wildlife animal reservoirs to humans, creating a local disease cluster. Stage three: the pathogen's uncontrolled replication spreads disease through sustained human-to-human transmission on a global scale, reaching new populations of uninfected people and causing a pandemic.

and public health measures [34]. The continued threat of emerging pandemic pathogens is disruptive to global communities—socioeconomically, politically, and medically—but continued international funding and collaboration can alleviate the burden.

Once a new or high-risk pathogen is identified through screening or surveillance, modern epidemiological techniques can be used to interrogate the pandemic threat. Mathematical modeling of climate data, animal migrations, and human activities can forecast transmissibility, asymptomatic or pre-symptomatic spread, and overall population risk. Additionally, the integration of smartphone technologies aid symptom monitoring, quarantining, or contact tracing. These early prediction models and technological advancements may identify populations benefitting from prompt and/or stricter interventions. Furthermore, laboratory studies provide valuable information for human infection potential and may translate to preclinical evidence for the development of therapies. These anticipatory investigations allow for timely interventions and early, sophisticated understanding of mechanisms that may help halt the spread of emerging pathogens of pandemic potential.

How do we slow the spread?

Anticipatory actions alone are limited in their effectiveness to slow the spread of a pandemic. Improvements and adherence to public health measures, widespread accessible testing, and clear communication to the public are indispensable tools for intercepting infections and preventing pandemic spread. Public health measures such as quarantines, travel

restrictions, wearing masks (for pathogens that transmit through air), and universal screening of healthy individuals indisputably slow the spread of pandemics [35]. As spotlighted at the beginning of this article, the universal recommendations during the COVID-19 pandemic closely mirrored the basic recommendations during the flu pandemic of 1918. At that time, public health officials directed individuals to avoid others, especially the ill, as a form of social distancing, wear face covers, and open windows for air ventilation. The congruence of the public health recommendations from today and a century ago underline that simple measures taken by everyone are the most effective to prevent escalating spread. Furthermore, lawmakers may consider examining data regarding the impact each individual public health measure has on the health of the population, informing public health and economic policies, weighing risk to an individual's rights and social harms.

Complementary to careful investigation and deployment of effective public health measures, widespread infectious screening of the healthy public is key to identifying and isolating asymptomatic cases, thus limiting pandemic spread. Limitations of testing are unavoidable: sick people will be missed by mass screening measures when the testing denominator is large. Thus, while the effectiveness of widespread screening stands up alone (assuming effective deployment), this tool is most effective when coupled with follow up measures. Directed testing naturally follows screening and who gets tested also matters. Vulnerable populations (racial and ethnic minorities, the elderly, and citizens of low socioeconomic status) have

been disproportionately affected by all modern pandemics [36]. During the COVID-19 pandemic, testing capacity in affluent communities was far greater despite targeted efforts in high-risk but low-resource neighborhoods [37]. There are multiple reasons, both for risk of infection and likelihood of getting tested. The most common testing barriers include fear, anticipated stigma, loss of employment, cost, accessibility, or the perceived burden of receiving a positive test result [38]. By the measures of equitable access to testing and high levels of comfort of individuals being tested, no pandemic surveillance program has ever been effective. A shift to cheaper, simpler, faster, at-home tests would circumvent a majority of these barriers [39,40]. Rapid diagnostic tests, including at-home tests have not achieved the same accuracy as standard testing [41]. However, the tradeoff of rapid identification of positive cases, greater societal access to, and more frequent testing would outweigh the intrinsic test limitations. Thus, we propose ongoing financial incentives for developing the scaffolds for at-home and rapid diagnostics which might include masks with built-in rapid tests, saliva or exhaled breath-based tests, or other cutting-edge testing strategies [42]. Further development of pipelines to support citizens with positive test results could rapidly change the course of the next pandemic for the better.

Communication is the foundation of all pandemic countermeasures. Clear messaging is essential to both ensuring the general public understands the basis of public health measures and the individual's responsibility to comply. Clear and consistent messaging from public agencies sharing both scientific and policy successes and failures provide transparency and respect to the public. The International Network for Government Science Advice argues for utmost transparency of pandemic epidemiological data (i.e. number of positive cases, number of deaths, etc.), as well as how these data were acquired and how predictive models are built [43]. Early transparency regarding clusters of new, severe pneumonias both during SARS in 2003 and COVID-19 in 2019 allowed coordinated effort to sequence the viral genomes, institute strict public health measures, and develop early testing, measures which certainly curtailed the SARS pandemic and COVID-19 in some countries. In fact, one recent study found that communicating uncertainty about facts increases the public's perceived uncertainty about these facts, however this is only accompanied by a small decrease in overall public trust [44]. Thus, we strongly recommend open global communication, close evaluation of public health messaging, and constant re-evaluation of public policy.

How do we speed countermeasure development?

While surveillance, testing, and non-pharmaceutical public health interventions are critical to slowing the pace of infectious disease transmission, medical countermeasures such as therapeutics and vaccines are essential for treating infected individuals. During an epidemic or pandemic, the rapid development of medical countermeasures is particularly important, especially when physicians lack treatment options beyond supportive care. Although speed is essential

when developing medical countermeasures, ensuring safety and efficacy is paramount. To this end, critical scientific development priorities, such as the Apollo Project for Biodefense, and regulatory reforms are establishing stable pipelines for developing novel therapeutics and vaccines for modern pandemics [45,46].

Prior to COVID-19, the shortest duration of a vaccine's development was four years for measles. The COVID-19 pandemic accelerated the usage of novel vaccine platforms, such as messenger RNA (mRNA) and viral vector vaccines, that utilize an interchangeable antigen component (which directs immunity against a specific pathogen) built into a fixed scaffold and delivery system (such as an mRNA construct or adenoviral vector) [19]. These vaccine platforms are considered to be "plug and play" vaccines that are defined by the ability to be rapidly designed and redesigned, changing the genetic sequence of the antigen component without altering the scaffold to account for new pathogen threats, including emerging variants of an infectious disease (Fig. 4) [47]. Template redesign can be straightforward, but the process of target identification and optimization is not. The history of the Moderna COVID-19 vaccine began long before COVID-19 as a project to leverage mRNA technology for another coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV) [48]. The infrastructure and expertise already existed to translate knowledge of designing prior coronavirus vaccines and apply them rapidly to COVID-19.

Success from the efficient development of coronavirus "plug and play" vaccines could be translated to other pathogens. Efforts are now underway to apply mRNA vaccine technology to the development of other viral vaccines and a malaria (parasite) vaccine. Building a library of prototype vaccines targeting pathogens of pandemic potential (including those identified through surveillance efforts) would contribute to an arsenal of preventative tools. Prior to an outbreak, these prototype vaccines can be designed to serve as scaffolds for vaccine design for related viruses and be brought through preclinical studies and early-stage clinical trials to determine their safety and suggest efficacy. In the event of an outbreak, the vaccine candidates could be modified and launched into later stage trials [49]. With concomitant rapid bridging studies confirming the new candidate vaccine's safety profile, months would be shaved off the vaccine development timeline. The key is to start this development before the next pandemic starts. The capabilities of prototype vaccines could be expanded by focusing research on vaccines that target multiple viruses within the same family, such as pan-coronavirus vaccines or universal flu vaccines [50].

In the case of both therapeutics and vaccines, there is much to be learned about conducting rapid, controlled clinical trials during an infectious disease outbreak. Flaws in the design of the AstraZeneca COVID vaccine trial undermined confidence in the vaccine and prevented regulatory approval in the U.S. [51]. At the same time, no clinical trials addressed strategies for dose sparing (providing first doses and delaying second doses of a two-dose vaccine) or mixing-and-matching

Figure 4: A model for integrating surveillance and countermeasure development that can be rapidly deployed during an outbreak. (a) Pathogen surveillance (including metagenomic sequencing (i.e. sequencing genomes from a sample of multiple organisms), syndromic surveillance, and other measures) is used to identify pathogens and pathogen families with pandemic potential. (b) Prototype diagnostic and vaccine scaffolds for pathogen families with pandemic potential are developed. (c) During an outbreak, specific genetic sequence information from the pathogen is input into the scaffold to create a pathogen specific diagnostic or vaccine. (d) Newly-developed, specific medical countermeasures can then be evaluated for efficacy and emergency use. Created with BioRender.com.

of different vaccines—both strategies that are being used with limited clinical data to support their use. In the future, regulators could establish standardized clinical trial designs, improve information sharing between investigators, and design publicly-funded trials that explore combinations of different vaccines that individual companies might not otherwise fund.

The scientific and clinical knowledge to rapidly develop medical countermeasures during an infectious disease outbreak exists. However, that knowledge should continuously evolve as more technology is developed. The cost of developing new therapeutics and vaccines and shepherding them through early stage clinical trials is expensive [52]. While government financed pre-purchase agreements during the COVID-19 pandemic absorbed many of these costs, preparing for the next pandemic requires long-term funding. Improving the capabilities of rapid therapeutic and vaccine development platforms can be accomplished by increasing support for agencies, such as the Biomedical Advanced Research Development Agency, Defense Advanced Projects Research Agency, and National Institutes of Health, that fund research into these systems. Improving clinical trial

design and launching early stage clinical trials for therapeutics and vaccines that are not immediately necessary requires significant investment in clinical research capabilities and rethinking our traditional paradigms of trial funding. In the absence of an immediate market for a therapeutic or vaccine, additional government support for and funding of these trials may be necessary. Fundamentally, this would take the government-led funding model used for COVID-19 vaccine development and apply it to “Disease X”—some might think of it as “plug and play” with funding—to prevent future pandemics. Without these steps to invest in therapeutic and vaccine development, we may find that we do not have the tools to fight the next pandemic, which may be more severe than the current one.

Conclusions

Novel and reemerging infectious diseases of zoonotic origin have been a major threat to human lives for millennia. With ongoing urbanization, deforestation, and human-animal contact, the threat of the next pandemic looms large and soon. While new infectious diseases cannot be prevented, their spread and destruction can be contained. Preemptive adoption of countermeasures such as increased pathogen

surveillance, global data sharing, development of scaffolds for diagnostics, therapeutics, and vaccines will play a large role moving forward. We hope to impart the gravity of preemptive solutions for the protection of human lives in the 21st century and beyond.

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