STAFF PERSPECTIVE

Ignoring Emerging Infectious Diseases: The Fatal Error That Could Lead to the Next Pandemic

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Key Points

- Emerging Infectious Diseases (EIDs) are a group of novel or re-surging infectious pathogens which primarily originate from animal populations.
- Many EIDs have a pandemic-causing ability and should be a top priority for governments worldwide.
- The primary strategies that should be implemented to prevent a pandemic caused by emerging pathogens revolve around preventing the transfer of zoonoses via diligent surveillance methods involving classical tools, data science, and artificial intelligence.
- The equitable use of mRNA vaccine templates can decrease the spread, morbidity, and mortality of viral and possibly other pathogenic EIDs.
- Governments must invest in creating stable healthcare systems and well-equipped research facilities to handle the burden of EID outbreaks.

Keywords: Emerging Infectious Diseases, Pandemic Preparedness, Vaccines, Epidemiology

Introduction

In an October 2019 interview, the Director-General of the World Health Organization, Dr Tedros Adhanom Gebreyesus, warned that the world was dangerously unprepared for the next flu pandemic[1]. At the time, this message was not taken seriously. 25 months later, global healthcare systems and economies suffered substantial damage, and over 5 million people died of Coronavirus Disease 2019 (COVID-19)[2]. Despite the harm that has already been done, it is unproductive to belabour the past and assign blame. Instead, nations should reflect on COVID-19 and their response to the initial outbreaks of the virus.

Despite almost 2 years of first-hand experience, most countries remain unprepared for the next pandemic. Even before COVID-19, significant funds went into infectious disease research, however, the outcomes of considerable investments did not translate into effective pandemic preparedness plans. In their 2020 study, Head et al. found that between the years 2000 and 2017, G20 countries invested USD 104.9 billion into infectious disease research[3]. Between these years, G20 countries failed to eradicate any Emerging Infectious Diseases (EIDs) and, in 2020, failed to prevent the COVID-19 pandemic. Considering that it took the United States only 0.288% of the G20 investment to eradicate smallpox in a period of ten years[4], it would be expected that more progress would have been made in tackling EIDs. The failure of the G20 countries is primarily due to two reasons: poor strategy, and inadequate allocation of funds. Head et al. reported that the highest fraction of investments went to HIV, while EIDs like ebolaviruses or coronaviruses only received funds in situational circumstances (e.g. in response to an outbreak)[3]. Despite the world's researchers and healthcare systems increasing their investments and research efforts on coronaviruses, many EIDs continue to be ignored by the scientific community. These diseases pose a constant threat to global health and well-being. The 'sit-and-wait' approach, which ultimately led to COVID-19, needs to be reformed with a greater emphasis on proactive prevention methods rather than post-outbreak reactions. However, before drafting policy plans on how to effectively intercept outbreaks, it is important to return to the fundamentals of EID biology and epidemiology to truly understand the dynamics of these pathogens.

The Current State of EIDs

Definition

EIDs are contagious pathogens which have either been identified for the first time in a specific community or have previously existed but are increasing in prevalence or geographic radius[5]. The US National Institute of Allergy and Infectious Diseases (NIAID) classifies EIDs into three categories based on their threat to public health[6]. Category A pathogens require particular attention from a public health point of view as they are easily transmitted and have high mortality rates. These pathogens are characterized by their ability to cause outbreaks of varying severity, with some having pandemic-causing ability. Examples of diseases and pathogens that fall into this group are anthrax (*Bacillus anthracis*), Ebola Virus Disease (Ebola virus), and Dengue Fever (Flaviviruses). Category B infections have lower transmissibility than those in category A, may result in moderate morbidity and mortality rates, and require some additional tools for surveillance. Some diseases in this group are Hepatitis A (Hepatovirus A), West Nile Fever (West Nile Virus), and Zika Virus Disease (Zika Virus). The pathogens classified in group C may evolve in the future to become more transmissible or virulent and pose a large pandemic threat. Some examples of these pathogens are prion diseases, antibiotically-resistant bacteria, coronaviruses and HIV. While there is vast diversity in the pathogens that are considered EIDs, one similarity that almost all of them share is that they are passed from animals to humans.

Transmission—Zoonosis

Zoonotic diseases are introduced into the human population via direct contact with infected animals, water sources, food sources, or environmental factors[6]. Zoonotic pathogens are grouped into five stages based on how they spread. Stages 1 and 2 diseases may only be acquired from animals, while stage 5 pathogens are endemic human diseases (e.g. can only be spread between humans). Pathogens that can infect both humans and animals at different rates are grouped into stages 3 and 4. Since SARS-CoV-2, the virus causing COVID-19 was likely passed onto humans from bats via an intermediate host, zoonoses have become a topic of interest in the scientific community.

When an EID is passed onto a human host, it can only spread further if it is able to effectively spread between individuals. Modes of transmission differ radically between diseases, but some routes are common to all EIDs. Between humans, pathogens can be spread through direct contact, respiratory droplets, and bodily fluids, amongst other methods. The rate of transmission between various pathogens differs greatly, but there are certain human and environmental considerations that increase the risk of a spillover event and the subsequent spread of the infection between humans.

Factors Contributing to the Outbreaks of EIDs

Globalization has completely redefined the state of infectious diseases in the 21st century. Though international partnerships are at the heart of scientific and medical advancement, higher levels of human contact as well as changes to patterns of international travel have greatly contributed to the emergence of EIDs[7]. Indeed, in the early stages of the COVID-19 pandemic, air travel likely played a major role in the dispersion of SARS-CoV-2. In addition, global movement may lead to the introduction of vectors carrying pathogens to regions they previously did not inhabit via an intermediate human host. Perhaps the most important risk factor to consider is the increase in the international wildlife trade. As there is increased contact between humans and animals that may act as reservoirs of infectious pathogens, the risk of an infection being transferred is much greater. Most EIDs are zoonoses, so naturally targeting the international wildlife trade has been implicated as a possible deterrent to the outbreaks of emerging pathogens. When considering human risk factors in EID outbreaks, it is also critical to take into account host-pathogen dynamics. In many countries with ageing populations, there is a higher risk of EID spillover from animals to humans as more individuals experience immunosenescence in old age and do not mount a strong immune response. The burden of EIDs on these nations may also be greater due to the increased morbidity and mortality associated with many EIDs and advanced age.

Moving away from human factors, a pathogen's environment may also play a role in driving outbreaks. For instance, it is likely that with climate changes, infectious agents that favour tropical environments will evolve and become more prominent. Environmental changes may also impact a pathogen's reservoir, and for vector-borne diseases, their transmission-related characteristics.

The risk factors for EID outbreaks must be carefully considered while planning policy for pandemic prevention. While it may be useful to tackle them individually, most public health experts have suggested that preventing spillover events, the core of EIDs, may alleviate the need to modify other human behaviours. At the same time, focusing solely on zoonoses is unproductive, and countries must be urged to evaluate and invest in other pandemic-preparedness measures.

Tackling EIDs

In the past, global strategies for dealing with EIDs have relied on the 'sit-and-wait' approach[8]. If an outbreak occurs, governments impose local or national restrictions while the scientific community focuses their efforts on drug and vaccine development. This strategy has proven to be ineffective. Even slight delays in detection and the subsequent response, for example, due to long pathogen incubation periods, or the lack of appropriate diagnostic tools, can cause considerable damage to healthcare systems and economies. The lack of a proper preparedness plan can allow pathogens to transition from being rare tropical infections to top priorities of global well-being in a matter of days. Despite the lessons learnt from COVID-19, the world remains unprepared to tackle the next emerging pathogen. While there are differing opinions on how best to prepare for or respond to infectious outbreaks, experts agree on several overarching strategies which would greatly benefit countries' responses to clusters of pathogens: i) preventing the spread of zoonoses, ii) vaccine development, and iii) investment in healthcare systems.

Preventing the Spread of Zoonoses & Surveillance

Over the past two years, addressing zoonotic pathogens has dominated the keynote speeches and information booklets of medical conferences worldwide. While the literature contains differing opinions on how best to tackle zoonotic transfer, there are common topics that are emphasized in numerous studies.

The cessation of the illegal animal trade is a logical step to reduce the risk of zoonotic events. Due to increased globalization and international travel, the movement of pathogens outside of their normal ecological and geographical boundaries via animal hosts is inevitable. Unfortunately, most governments do not have an agency that detects pathogens in imported wildlife, creating a loophole which may lead to the emergence of EIDs[9]. Moreover, the legal wildlife trade was also identified as a potential risk factor for the transfer of zoonoses. It is likely that SARS-CoV-2 emerged in a Wuhan wet market which cultivated perfect conditions for the transfer of an animal coronavirus to humans[10]. Based on the severe risk it poses, it has become clear that the best option to decrease the risk of zoonosis would be to terminate all wildlife trade[9]. However, this approach is highly unrealistic, and many countries would refuse to agree to these terms. Instead, a 'clean trade' scheme should be implemented to initiate safe and diligent strategies in wildlife commerce, including policy-making and surveillance.

One of the major strategies proposed to combat zoonotic diseases is the umbrella approach suggested by Shiferaw et al[11]. The plan brings together governments, scientific/medical personnel, as well as the general public to improve the state of EIDs via surveillance, education, laboratory work, and legislation. Despite some success of these methods in controlling endemic zoonoses, it may be difficult to implement them in the monitoring of emerging infections. Most novel EIDs arise in low-income countries which do not have the funds or resources to carry out the plan outlined by Shiferaw et al. To combat this issue, Ellwanger et al. have suggested that only the highest risk animal and human populations should be monitored for emerging infections, decreasing the financial burden on developing countries[12]. This targeted surveillance would focus on pathogens that are known to have crossed the species barrier and their animal hosts which make the most contact with humans (companion animals, livestock, some wild animals). In addition, specific human populations, specifically those who are in close contact with wild animals and a select group from the general population, may be closely monitored for infection. This method may be effective for already known pathogens, yet falls short of identifying novel pathogens, meaning that other prevention strategies are required.

Following COVID-19's exposure to poor surveillance concerning infectious diseases, multiple approaches using new technology have been suggested to ameliorate the monitoring of emerging pathogens. Data science approaches use human behaviour patterns, clinical records, as well as scientific literature to track and model the courses of EID outbreaks[13]. The findings of these studies could be used to inform how governments should handle clusters of disease, travel restrictions, and quarantine measures. Data science may also be used to monitor the movements and infections within non-human disease hosts. Akinyi et al. monitored non-human primates in Kenya for gastrointestinal protozoa and viruses using simple diagnostic tools such as microscopy, ELISA, and PCR[14]. While these tools may pose financial issues for laboratories in lower-income countries, they are more cost-effective than techniques such as sequencing and yet produce similar diagnostic value. While data science strategies require a large quantity of trained workers as well as robust laboratories, they can be effectively employed in tackling a large variety of human viruses such as SARS-CoV-2, Ebola virus, and HIV, and may be used for other non-viral pathogens in the future. Vigorous monitoring of infection dynamics among animal and human hosts allows for the rapid identification of pathogens but also has a prognostic value which facilitates accurate predictions of EID outbreak patterns.

Along with data science and traditional monitoring methods, artificial intelligence (AI) has also emerged as a new field in infectious disease biology. AI uses public health surveillance data to model infectious disease spread and conduct experimental analyses and evaluation which could inform public policy to establish optimal infectious disease control measures[15]. So-called 'hybrid models' which take into account various environmental factors in addition to human and animal behaviour have also been suggested to more accurately model pathogen spread under different climatic conditions. These prediction methods have already been successful in monitoring viral and parasitic outbreaks and holds promise in the surveillance of other types of EIDs.

It is conceivable that data science, AI, and traditional methods used in combination may be the key to preventing the next type of zoonotic event as they take into account all risk factors and contributors to EID spread. Findings from various studies have already informed databases evaluating zoonosis risk. For example, the *Spillover* database ranks known viral pathogens based on eight factors: host genetics, host epidemiology, host ecology, environmental factors, virus genetics, virology, virus ecology, and virus epidemiology. In the future, these databases may be used to classify novel pathogens, but also monitor the currently known ones to identify those at highest risk for a zoonotic transfer[16].

Vaccine Development

Vaccination is an effective tool used to decrease the transmission and mortality rate of a pathogenic infection. The testing and manufacturing of a vaccine used to be a lengthy process; usually, it would take about ten years to produce a suitable antigen and to group it with the correct adjuvant and delivery method[17]. The COVID-19 pandemic markedly accelerated this process as the vaccines used to fight SARS-CoV-2 were synthesized and brought through meticulous clinical testing in less than a year. The molecular mechanisms behind mRNA vaccines allow for this rapid development. mRNA vaccines only differ by the RNA sequence, not by the method of administration, meaning that their base sequence can be quickly modified should a new pathogen emerge. In addition, the adjustable quality of mRNA vaccines allows them to combat mutations in pathogens as their base sequence can be altered to counter the effects of genetic variants[18]. Editing the mRNA is much simpler than editing an entire protein or its subunits, simplifying and accelerating the vaccine production pipeline. Multiple mRNA vaccines can also be manufactured in the same facility, allowing for efficient mass production. So how can we harness the benefits of mRNA vaccines to combat emerging pathogens? The best proposed method is a blueprint vaccine which can be modified based on a pathogen-specific antigen. This prophylactic measure could further reduce the time between outbreak and vaccine availability as the vaccine would already have undergone rigorous testing – the only modification that would have to be made is the genetic code. Some experts argue that despite the success of mRNA technology in the battle against SARS-CoV-2, there is not enough evidence to optimistically declare that this methodology could function against other pathogens[19]. Bacteria are far more structurally and functionally complex than viruses, making it difficult to synthesize an antigen with high enough levels of immunogenicity. The same line of argument can be used for emerging infections caused by parasites characterized by their elaborate life cycles and immune evasion. In summary, while mRNA vaccines may not be applicable to all pathogens, their high effectiveness logistical advantages make them a promising tool in the fight against viral EIDs.

Despite the favourable clinical outcomes against pathogens, the success of vaccination is often limited by the issue of proper vaccine distribution. Global vaccine equity is one of the greatest challenges that we are currently facing and will continue to confront in the future. The primary aetiology of vaccine inequity is caused by a small supply and the unjust allotment of doses[20]. While the synthesis and production of mRNA vaccines are fast-moving, supply-chain issues and the economic challenges that came with the pandemic limited the supply of doses of many vaccines which are available on the market. Additionally, in the case of SARS-CoV-2 vaccines, high-income countries pre-ordered large quantities of doses for their populations while low-income countries received only 1.2% of the world's vaccines despite making up 40% of the global population. The unfair allocation of vaccines leads to infection hot spots in areas with poor vaccine uptake. Additionally, areas with low vaccination rates could be the source of new viral variants as higher levels of intracellular replication is responsible for higher mutation frequencies. In the short-term, strategies to improve the state of vaccine distribution are to re-allocate stockpiles to areas with the highest infection rates and lowest vaccine uptake. In the long-term, plans should seek to target areas which are at risk of housing severe outbreaks before an infectious wave takes over.

In summary, as demonstrated in the COVID-19 pandemic, mRNA vaccines are an effective manner of combatting emerging viral pathogens. Their ease of manufacture and flexibility could greatly contribute to rapidly addressing explosive outbreaks. However, the unjust distribution of vaccines puts a brake on its success as a strategy for combatting EIDs. Additionally, there may still be gaps between the time at which an outbreak occurs, and when a vaccine is made available. Therefore, it is also crucial to invest in healthcare systems capable of effectually caring for a population until a vaccine is fully approved.

Investing in Healthcare Systems & Preparedness Plans

High-income countries that remain overly confident in their strong healthcare systems are not actively preparing for the next pandemic in terms of both surveillance and response measures[21]. This flaw was particularly seen when many high-income nations, including Ireland, saw their healthcare systems crumble during various phases of the COVID-19 pandemic. Inadequate numbers of clinicians and healthcare professionals, as well as burn-out and a lack of hospital beds and medical equipment led to many hospitals being stretched thin and unable to provide enough care to patients. Peaks of infection cannot always be predicted, so it is critical to be on constant lookout for possible outbreaks as even the strongest of systems have a breaking point. A key feature of a strong pandemic response is the establishment of well-equipped and personnel-rich scientific, medical, and translational institutions[22]. Continuous investment in healthcare systems may reduce patient mortality should an outbreak occur. Additionally, higher expenditure on research facilities would accelerate the creation of safe and effective vaccines and other pharmacological interventions. It is important to note that even with substantial preparations for a pandemic, it is still crucial to employ classical public health manoeuvres to drive down the spread of an EID should it emerge.

Conclusion

In summary, EIDs are a constant global threat that is frequently ignored by the scientific community and governments across the world. Increased globalization and contact between humans as well as animal-to-human contact have greatly increased the risk of zoonotic events and subsequent EID outbreaks. Despite over two years of first-hand experience, the world remains severely unprepared to tackle the next pandemic. The 'sit-and-wait' approach needs to come to an end, and proper pandemic policies need to be implemented. Zoonoses should be targeted using robust surveillance tools including classical diagnostic measures, data science methods, and artificial intelligence.

In addition, an mRNA vaccine blueprint should be established before an outbreak occurs to minimize the time between outbreak onset and vaccine availability. Vaccine equity should also be tackled by appropriate needs-based distribution doses. Finally, governments should provide substantial funding and recruit sufficient personnel to tackle an EID outbreak. Epidemiological measures and organized health facilities should be appropriately employed to reduce transmission and mortality before a vaccine becomes available. We need to retrace our steps with COVID-19 and use the lessons learnt to prepare for the next pandemic. Diseases do not respect borders or take turns, and for this reason, this piece is not merely an opinion, but a call for action. ◄

Declarations

Karlo Vidovic is a staff writer on the editorial board of the TSMJ, and was asked to contribute an invited Staff Feature to the TSMJ Volume 22. The author declares that the article was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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