REVIEW ARTICLE

Unveiling Disease X: Strategies for Tackling the New Frontier of Infectious Diseases

Yuda Fei¹ and Jing Huang¹,*

Abstract

Disease X stands as a symbol for a subset of emerging infectious diseases rising to prominence as a significant challenge to global health security. This comprehensive review delves into the historical context, precise definition, and illustrative case studies of disease X, including notable examples, such as COVID-19, SARS, and Ebola. The discussion then transitions to an examination of the potential origins of disease X, with a particular focus on zoonotic pathways and the influence of environmental factors. The review concludes with a suite of proposed strategies aimed at the prevention and containment of disease X, emphasizing the critical role of vigilant surveillance, swift response mechanisms, and the necessity of fostering international cooperation.

Keywords: disease X, zoonotic transmission, surveillance, response, cooperation

INTRODUCTION

As we explore the extensive annals of medical literature on unknown diseases, the terms “X disease” and “disease X” frequently emerge, each carrying distinct implications. X disease typically refers to a specific illness or condition that has been identified and named, with X signifying the actual name of the disease. The earliest recorded mention of an X disease dates back to 1920 [1], detailing the epidemiology of acute encephalomyelitis in Australia. In contrast, Disease X is a broader concept introduced by the World Health Organization (WHO) to represent a hypothetical or unknown pathogen with potential to cause a severe global epidemic or pandemic [2]. Disease X symbolizes an unidentified pathogen with the potential to trigger a significant global epidemic. This concept emerged in response to the realization that emerging infectious diseases pose a formidable threat to global health security [3], as demonstrated by the following outbreaks severe acute respiratory syndrome (SARS); Middle East respiratory syndrome (MERS); Ebola virus disease; Zika virus disease; and most prominently, the COVID-19 pandemic [4-8]. Notably, the frequency of infectious disease outbreaks has tripled over the past 40 years [9].

On 18 November 2022 the WHO convened a gathering of over 300 scientists to review data on more than 25 virus families and bacteria, including the enigmatic disease X [10]. The WHO hoped to lead a comprehensive international initiative for revising the catalogue of critical pathogens (entities capable of triggering outbreaks or pandemics), the goal of which was to guide global investment, research, and progress with a particular focus on vaccines, diagnostics, and therapeutics. Disease X underscores the imperative for preparedness and vigilance against novel and unforeseen infectious agents.
(pathogen X), highlighting the need for a robust global health infrastructure capable of swiftly responding to emerging threats [2].

Although disease X has an unknown etiology, based on past knowledge, we can still identify some high-risk viral families. Among approximately 24 families of viruses known to infect humans, there are 6 specific families (Coronaviridae, Adenoviridae, Paramyxoviridae, Orthomyxoviridae, Poxviridae, and Picornaviridae) that possess characteristics which make them strong candidates for triggering future pandemics [9]. Although respiratory- or airborne-transmitted viruses are considered the most likely pathogens to cause the next global pandemic, some bacteria, especially those with pan-drug resistance, possess characteristics that could lead to a global public health crisis [11]. Additionally, fungi, protozoa, and even prions have the potential to cause outbreaks and epidemics within some geographic regions [12-14].

EXAMPLES OF DISEASE X

COVID-19: the global pandemic

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has emerged as one of the most significant global health crises in recent history [4,15]. The unprecedented scale and impact of the COVID-19 pandemic have exposed the vulnerabilities of global health systems and underscored the need for robust preparedness and response mechanisms [16,17]. The rapid spread of the virus, facilitated by international travel, urbanization, and population density, has emphasized the interconnectedness of modern society and infectious disease dynamics [18,19].

COVID-19 has presented a myriad of challenges for public health authorities, healthcare systems, and governments worldwide. The virus has exhibited a wide spectrum of clinical manifestations, ranging from mild respiratory symptoms-to-severe pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ failure [20]. Vulnerable populations, including the elderly and those with underlying health conditions, have been disproportionately affected by the virus [21,22]. Efforts to control the spread of COVID-19 have included widespread testing, contact tracing, quarantine measures, and social distancing guidelines [16]. However, containment efforts have been hampered by factors, such as asymptomatic transmission, limited testing capacity, and vaccine hesitancy. The development and distribution of vaccines against COVID-19 have represented a significant milestone in the pandemic response, offering hope for controlling transmission and mitigating the impact of the virus [22,23]. Despite vaccination efforts, the emergence of new variants of COVID-19 has raised concerns about vaccine effectiveness and the potential for future waves of infection [19,24,25]. Additionally, disparities in vaccine distribution and access have underscored the need for global solidarity and collaboration in addressing the pandemic [26].

As the COVID-19 pandemic continues to evolve, ongoing research efforts are focused on understanding the viral transmission dynamics, immune response, and long-term health effects [27]. Lessons learned from the pandemic will inform future preparedness and response efforts, emphasizing the importance of investing in resilient healthcare systems, pandemic preparedness, and international cooperation [16].

SARS: lessons learned from a past outbreak

The SARS outbreak in 2002-2003 serves as a pivotal event in understanding emerging infectious diseases and pandemic preparedness [8,28]. SARS presented several challenges to public health authorities, including rapid transmission within healthcare settings, a high case fatality rate, and the potential for international spread through air travel [29]. The outbreak highlighted the importance of timely detection, effective communication, and coordinated response efforts in containing emerging infectious diseases.

Following the SARS outbreak significant efforts were made to enhance global preparedness for future outbreaks. The WHO established the International Health Regulations (IHR), a legally binding framework aimed at improving global health security by facilitating early detection, reporting, and response to public health emergencies [30]. Additionally, investments were made in research and development of diagnostics, therapeutics, and vaccines targeting coronaviruses, including SARS-CoV. The outbreak of SARS served as a stark reminder of the potential for emerging infectious diseases to cause widespread harm and disruption. The lessons learned from SARS continue to inform pandemic preparedness efforts and underscore the importance of sustained investment in global health infrastructure [31].

Ebola: a persistent threat in Africa

Ebola virus disease (EVD) is a severe and often fatal illness caused by the Ebola virus, a member of the Filoviridae family. Since its discovery in 1976 in what is now the Democratic Republic of the Congo (DRC), EVD outbreaks have occurred sporadically in Central and West Africa, with devastating consequences for affected communities [32]. The largest outbreak in history occurred in West Africa from 2014–2016, primarily affecting Guinea, Liberia, and Sierra Leone, resulting in >28,600 reported cases and >11,000 deaths [7,33]. EVD outbreaks are characterized by rapid onset, a high case fatality rate, and the potential for nosocomial transmission, particularly in healthcare settings with limited resources and infection control measures [7,34]. The Ebola virus is primarily transmitted through direct contact with the blood, bodily fluids, or tissues of infected individuals or animals, such as fruit bats, which are believed to be natural reservoirs of Ebola virus [35].

Efforts to control Ebola outbreaks have been hindered by various factors, including weak healthcare
infrastructure, political instability, community mistrust, and logistical challenges in implementing control measures [36]. Deployment of experimental vaccines and therapeutics has shown promise in recent outbreaks, offering hope for more effective control and containment strategies [37].

Despite significant progress in understanding the epidemiology and pathogenesis of Ebola virus, the risk of future outbreaks remains a persistent threat in Africa [38]. Continued investment in surveillance, preparedness, and response capacity is essential for mitigating the impact of Ebola virus and other emerging infectious diseases on vulnerable populations [39–41].

POSSIBLE SOURCES OF DISEASE X

Zoonotic transmission: bridging the gap between animals and humans

Zoonotic diseases, which transmit from animals-to-humans, have been a persistent threat throughout human history. These diseases have caused widespread devastation, claiming lives, disrupting economies, and challenging public health systems [42]. Among the myriad of infectious diseases, disease X has garnered particular attention in recent years. While disease X itself remains speculative, the concept embodies the looming threat posed by zoonotic diseases and the urgent need for preparedness and response strategies.

Zoonotic transmission occurs when pathogens, such as viruses, bacteria, parasites, or fungi, jump from animals-to-humans. This spillover can happen directly through contact with infected animals or indirectly through vectors, such as mosquitoes, ticks, or fleas [43]. A pathogen that is transmitted from animals-to-humans can lead to repeated transmission among people. This can occur through vector transmission, contact transmission, or via the digestive and/or respiratory tracts, resulting in human-to-human transmission and gradually evolving into a human-to-human infectious disease. Respiratory transmission poses the greatest risk, as evidenced by the spread and impact of the novel coronavirus in recent years. Zoonotic pathogens may undergo genetic mutations or reassortments that enable them to infect and spread among human populations efficiently. Factors facilitating zoonotic spillover include ecologic changes, human encroachment into wildlife habitats, agricultural practices, wildlife trade, and climate change [44].

Zoonotic diseases have a profound impact on public health, economics, and ecosystems. In addition to the direct toll on human health, zoonotic diseases disrupt food systems, trade, tourism, and livelihoods. Outbreaks in livestock populations devastate agricultural economies, leading to food shortages and economic losses for communities reliant on farming and animal husbandry. Furthermore, the fear and stigma associated with zoonotic diseases can have a lasting social and psychological impact on affected populations.

The interface between humans, animals, and the environment plays a crucial role in zoonotic transmission dynamics (Fig 1). Encroachment into natural habitats, deforestation, and urbanization bring humans into closer contact with wildlife, increasing the likelihood of disease transmission [43]. Moreover, the expansion of agriculture and livestock production leads to intensified interactions between humans and domesticated animals, which creates opportunities for pathogens to cross species barriers.

This transmission route highlights the importance of interdisciplinary collaboration between epidemiologists, veterinarians, ecologists, and anthropologists in surveilling, predicting, and mitigating emerging infectious diseases. By fostering interdisciplinary collaboration, strengthening surveillance systems, and promoting sustainable land use practices, we can better prepare for and respond to the next zoonotic threat. Understanding the dynamics of zoonotic transmission not only aids in early detection and response but also underscores the imperative of preserving biodiversity and ecosystems to safeguard human health.

Environmental factors: impact of deforestation, climate change, and urbanization

Environmental factors, including deforestation, climate change, and urbanization, have a critical role in shaping the emergence and transmission of infectious diseases, with implications for disease X. These factors induce changes in ecologic systems, alter wildlife habitats, and influence human behaviors, creating an environment where the spillover of pathogens from animals-to-humans become more likely [44–47]. A thorough understanding of the intricate relationship between environmental alterations and disease emergence is crucial for reducing the risk associated with disease X and other zoonotic threats.

Deforestation, the large-scale clearing of forests for agricultural, logging, or urban development purposes, is a leading cause of habitat loss and biodiversity decline. As forests are fragmented or destroyed, wildlife is pushed into closer proximity with human settlements, increasing the probability of zoonotic transmission [45]. Deforestation also disrupts natural ecosystems, leading to shifts in the populations and distributions of vector species, such as mosquitoes and ticks, which are responsible for transmitting pathogens to humans. Research has consistently linked deforestation with the emergence of infectious diseases, such as malaria, dengue fever, and Lyme disease. For example, deforestation in the Amazon rainforest is correlated with an increase in malaria cases due to the creation of breeding grounds for *Anopheles* mosquitoes, the vectors of malaria parasites [47]. Similarly, deforestation in southeast Asia is associated with the spread of the Nipah virus [46], a deadly zoonotic pathogen transmitted from bats-to-humans via intermediate hosts.

Climate change poses profound challenges for the distribution, abundance, and seasonality of infectious diseases [48–51]. The rise in temperatures, changes
Figure 1 | Emergence, transmission, prevention, and control of disease X.
The factors influencing emergence of disease X including environmental factors and human activities. The pathways of disease transmission involve the cross-species spillover from one animal species to another and from animals to humans (zoonotic transmission), and finally the disease becomes a human disease by human-to-human transmission. The various prevention and control strategies, including surveillance, rapid response, global collaboration, and addressing underlying drivers. This figure shows the complexity of disease emergence, the interconnectedness of environmental and human factors, and the importance of comprehensive strategies for prevention and control.
in precipitation patterns, and the increase in extreme weather events directly affect the life cycles and behaviors of pathogens, vectors, and reservoir hosts [52-55]. Climate change also influences human behavior and migration patterns, adding another layer of complexity to disease dynamics [56].

A significant impact of climate change is the expansion of the geographic range of vector-borne diseases [57]. Warmer temperatures improve the breeding success of mosquitoes and speeds up the development of pathogens within these vectors, leading to heightened transmission rates [58,59]. The spread of Zika virus, dengue fever, and Chikungunya fever has been connected to climate changes in the mosquito distribution driven by climate change.

Moreover, climate change can intensify issues of food and water insecurity, displacement, and poverty, all of which increase the vulnerability of populations to infectious diseases [60-62]. In regions where health systems are already strained and infrastructure is lacking, the effects of climate change on disease emergence are especially pronounced.

Urbanization, the process of population growth and migration to urban areas, significantly affects disease transmission dynamics [63-66]. Rapid urbanization can lead to overcrowding, inadequate sanitation, and limited access to clean water, all of which are ideal conditions for the spread of infectious diseases [67]. Urban expansion often involves conversion of natural habitats into built environments, increasing interactions between human and wildlife and the risk of zoonotic spillover.

The high density of populations in urban areas facilitates the rapid transmission of diseases through close contact and shared use of infrastructure [68]. Poor living conditions, inadequate hygiene practices, and limited healthcare access contribute to the emergence and spread of various infectious diseases, including respiratory infections, diarrheal diseases, and vector-borne diseases [69].

Furthermore, urbanization can lead to changes in ecosystems and disrupt natural habitats, resulting in alterations in wildlife behavior and distribution [63]. Urbanization brings wildlife to closer contact with human populations, which increases the potential for zoonotic transmission events.

In conclusion, deforestation, climate change, and urbanization are interconnected environmental factors that have a significant impact on the emergence and transmission of infectious diseases, including the hypothetical disease X. These environmental drivers alter ecosystems, disrupt wildlife habitats, and create conditions that facilitate zoonotic spillover events [70,71]. To mitigate the impact, a comprehensive approach is required that promotes sustainable land use practices, strengthens public health infrastructure, and addresses underlying socioeconomic disparities. In so doing, we can reduce the risk posed by disease X and other emerging infectious diseases in the future.

**PREVENTION AND CONTROL STRATEGIES FOR DISEASE X**

**Surveillance: early detection and monitoring**

Robust surveillance systems are paramount for the early detection and continuous monitoring of disease X and other emerging infectious diseases [72]. Surveillance entails the systematic collection, analysis, and interpretation of data regarding disease occurrence and transmission patterns [73]. This process is crucial for identifying outbreaks at their inception and monitoring disease trends over time, thereby enabling public health interventions that prevent disease spread and lessen the impact [74].

A cornerstone of effective surveillance is the establishment of robust reporting mechanisms for suspected cases [75]. Health facilities, laboratories, and providers are instrumental in identifying and reporting potential cases of disease X cases to public health authorities [76-78]. Timely reporting facilitates swift investigative actions and response measures, such as case isolation, contact tracing, and implementation of control strategies [79].

Beyond case-based surveillance, syndromic surveillance methods offer early warning signs of potential outbreaks by tracing trends in symptoms or health-seeking behaviors within the population [80]. These systems, often drawing on data from emergency departments, sentinel clinics, or electronic health records, can identify unusual patterns suggestive of an outbreak even before laboratory confirmation of the pathogen.

The integration of data from diverse sources, including clinical, laboratory, environmental, and animal health information, enhances the comprehensiveness and accuracy of surveillance systems. This One Health approach acknowledges the interconnectedness of human, animal, and environmental health, facilitating the early identification of zoonotic diseases, such as disease X [81].

Advanced technologies, such as genomics, remote sensing, and digital surveillance platforms, open new avenues for enhancing disease surveillance [82-84]. Genomic sequencing of pathogens allows for the rapid identification and characterization of new pathogens, aiding in targeted response efforts and the development of diagnostics, vaccines, and therapeutics. Remote sensing can monitor environmental changes and predict disease outbreaks by identifying ecologic factors that influence transmission, such as shifts in temperature or rainfall. Digital surveillance platforms, including mobile health apps and social media monitoring, offer real-time data on disease symptoms, travel patterns, and public sentiment, enabling a rapid response to emerging threats.

**Rapid response: coordinated efforts and emergency preparedness**

A rapid and coordinated response is essential for containing disease X outbreaks and minimizing the impact on public health and society [85]. Rapid response initiatives include a spectrum of activities, such as case management,
contact tracing, vaccination campaigns, and implementation of public health interventions, to curb disease transmission [86,87].

A key element of rapid response is the formation of emergency response teams and incident management systems at national, regional, and global levels [88]. These teams coordinate surveillance, laboratory testing, case investigation, and public communication during outbreaks [89,90]. Incident management systems streamline information sharing and decision-making, ensuring a prompt and effective response to threats, such as disease X [91].

Clear and transparent communication is vital during outbreaks, ensuring that the public, healthcare providers, and policymakers receive timely and accurate information [92-96]. Effective communication fosters trust in public health authorities and encourages adherence to control measures, such as quarantine and vaccination. Social media, press releases, and community engagement are essential in spreading health messages and countering misinformation during outbreaks.

Rapid response efforts also depend on established protocols and contingency plans that have been developed through comprehensive risk assessments and scenario planning exercises [97]. These plans detail the roles and responsibilities of key stakeholders, resource requirements, and logistic arrangements for deploying medical supplies, personnel, and equipment to affected areas. Regular drills and simulations evaluate the effectiveness of response plans and identify areas for improvement, which enhances preparedness for future outbreaks.

International collaboration is indispensable for coordinating rapid response efforts and mobilizing resources to support affected countries in need [97]. Global health organizations, such as the WHO, the Centers for Disease Control and Prevention (CDC), and Médecins Sans Frontières (MSF), provide critical technical assistance, expertise, and funding to bolster national capacities for outbreak response. Initiatives, such as the Global Outbreak Alert and Response Network (GOARN), facilitate the rapid deployment of international teams to assist countries in containing outbreaks and preventing cross-border spread [98].

**Global collaboration: sharing data and resources**

Global collaboration is essential in effectively confronting the challenges posed by disease X and other emerging infectious diseases. The sharing of data, resources, and expertise across borders is vital for early detection, rapid response, and coordinated efforts to contain outbreaks and prevent spread.

One pivotal aspect of global collaboration is the exchange of epidemiologic and genomic data on infectious diseases. Open access to data on disease occurrence, transmission dynamics, and genetic sequences empowers researchers and public health authorities to track pathogen spread, identify emerging threats, and assess the potential impact on human health. Initiatives, such as the Global Initiative on Sharing All Influenza Data (GISAID) and GOARN, promote data sharing and best practices among nations and international organizations [98,99].

Collaborative research efforts also stimulate innovation and accelerate the development of diagnostics, vaccines, and therapeutics for emerging infectious diseases [100]. Multinational research consortia unite scientists from various disciplines to investigate pathogen biology, host-pathogen interactions, and immune responses, leading to new intervention targets and countermeasure development [101].

Global collaboration also extends to capacity-building initiatives aimed at strengthening public health infrastructure and workforce development in resource-limited settings [102-104]. Training programs, technical assistance, and laboratory support help countries enhance the surveillance, diagnostic methods, and response capabilities, enabling more effective outbreak detection and control, and reducing reliance on external assistance during emergencies.

Finally, international frameworks and agreements provide a foundation for collective action and cooperation in addressing global health threats [104-106]. The IHR serve as a legal instrument for preventing, detecting, and responding to public health emergencies of international concern, guiding countries in their preparedness and response efforts and facilitating cross-border information sharing and collaboration [107].

**Addressing underlying drivers: tackling deforestation, wildlife trade, and climate change**

To effectively combat the emergence and spread of disease X and other zoonotic diseases, addressing the underlying drivers that contribute to emergence is crucial [108,109]. Deforestation, wildlife trade, and climate change are key environmental factors that facilitate pathogen spillover from animals-to-humans [110,111]. By implementing strategies to mitigate these drivers, we can reduce the risk of future pandemics and protect public health.

Deforestation, which leads to habitat loss and biodiversity decline, disrupts ecosystems and brings humans into closer proximity to wildlife [112]. The conversion of forests into agricultural land, urban areas, and infrastructure projects creates opportunities for zoonotic spillover by breaking natural barriers between wildlife habitats and human settlements [113]. To tackle deforestation, conservation efforts must focus on promoting sustainable land use practices, protect critical habitats, and enforce regulations to prevent illegal logging and land conversion. Additionally, initiatives to restore degraded landscapes and promote reforestation can help mitigate the impact of deforestation on disease emergence.

The wildlife trade, both legal and illegal, poses a significant risk for disease emergence by bringing humans into contact with wild animals carrying novel pathogens [114]. The trafficking of wildlife for food, traditional
Unveiling Disease X: Strategies for Tackling the New Frontier of Infectious Diseases

medicine, pets, and exotic products increases the likelihood of zoonotic spillover events as animals are transported across borders and come into contact with humans in crowded markets and trade hubs [115]. To address the wildlife trade, efforts should focus on strengthening regulations, enforcing wildlife protection laws, and combating illegal trafficking. Public awareness campaigns can also help reduce demand for wildlife products and promote alternative livelihoods for communities dependent on the wildlife trade.

Climate change exacerbates the risk of disease emergence by altering ecosystems, disrupting wildlife habitats, and influencing the distribution and behavior of vector species [116]. Rising temperatures, changing rainfall patterns, and extreme weather events create favorable conditions for the transmission of vector-borne diseases, such as malaria, dengue fever, and Lyme disease. To address climate change, global efforts must focus on reducing greenhouse gas emissions, transitioning to renewable energy sources and implementing adaptation strategies to enhance resilience to climate-related effects [117]. Additionally, initiatives to promote sustainable land management, protect natural habitats, and restore ecosystems can help mitigate the impact of climate change on disease emergence.

Therefore, addressing the underlying drivers of disease emergence, including deforestation, wildlife trade, and climate change, is essential for preventing future pandemics and safeguarding public health. Multisectoral and collaborative approaches are needed to tackle these complex challenges and mitigate the impact on human and environmental health. By promoting sustainable land use practices, protecting biodiversity, and reducing greenhouse gas emissions, we can create a healthier and more resilient future for all.

CONCLUSION

The emergence of disease X underscores the urgent need to address global health security threats and bolster preparedness and response efforts [118]. Disease X epitomizes the unpredictable and potentially severe nature of emerging infectious diseases. The ongoing COVID-19 pandemic serves as a stark reminder of the devastating impact of novel pathogens and the urgency of addressing disease X cannot be overstated. Failure to adequately prepare for and respond to future pandemics could result in catastrophic consequences for public health, economies, and societies worldwide. Proactive measures to mitigate the risk of disease X must be prioritized to ensure the resilience of global health systems and safeguard the well-being of populations globally [75, 79].

In light of the ongoing threat posed by disease X and other emerging infectious diseases, a concerted global effort is required to strengthen preparedness and response efforts [119]. This call to action includes the following key components: enhancing surveillance and early detection capabilities to promptly identify emerging threats; building robust public health infrastructure and laboratory capacity for rapid diagnosis and characterization of novel pathogens; strengthening international collaboration and information-sharing mechanisms for a coordinated response to outbreaks; investing in research and development of diagnostics, vaccines, and therapeutics for emerging infectious diseases; promoting One Health approaches that recognize the interconnectedness of human, animal, and environmental health in disease emergence and transmission; and addressing underlying drivers of disease emergence through multisectoral and collaborative efforts.

By prioritizing these actions and working together across borders and disciplines, the global community can enhance its resilience to future pandemics and protect the health and well-being of populations worldwide. Regrettably, the World Health Organization Pandemic Agreement continues to encounter challenges in achieving a conclusive consensus [120, 121].

ACKNOWLEDGMENTS

Our work was supported by the National Social Science Fund (contract no. CLA210281). We would like to express our sincere gratitude to KIMI and ChatGTP, the artificial intelligence assistants, for helpful discussion and valuable insight in the process of drafting this review and assisting with the linguistic nuances of English.

CONFLICTS OF INTEREST

No conflict of interests reported by the authors.

REFERENCES


