A Quest for Disease X: Origin, Location, and Mitigation

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Abstract. In February 2018, the World Health Organization (WHO) designated "Disease X" as a placeholder for a hypothetical and unidentified pathogen capable of potentially causing an epidemic in the future. The Covid-19 pandemic that unfolded recently has highlighted the emergence of a highly contagious Disease X, serving as a painful reminder of the potential risks we confront. This article aims to explore the emergence of Disease X, its possible origins, and proposes strategies to improve preparedness for such scenarios. Firstly, Disease X is probably a highly infectious zoonotic virus with RNA as its genetic material. Secondly, factors that may contribute to the emergence of the disease, including population density, ecological deterioration, and medical resources. Finally, barriers to the development of antiviral drugs and vaccines are examined, along with recommendations for social and ecological measures to enhance our preparedness for disease X.

Keywords: Disease X, RNA virus, highly infectious, Measures.

1. Introduction

Disease X, coined by the WHO in their 2018 announcement of the updated shortlist of blueprint priority diseases (Disease X 2022), epitomizes our scant knowledge of the forthcoming potential pandemic. (Scutti, 2018). COVID-19 was a wake-up call that galvanized us into action. However, are we adequately equipped to confront this looming menace? This essay delves into Disease X's emergence and potential location while proposing strategies for preparing for it. The first chapter stresses that Disease X will likely be a virus with zoonotic origins, RNA as its genetic material, and an accidental high infectiousness. In the second chapter, I explore factors that may contribute to the disease's emergence, including population density, ecological deterioration, and medical resources. Finally, I examine the obstacles to the development of antiviral drugs and vaccines while suggesting social and ecological measures that can reinforce our preparedness for Disease X. With Disease X's inevitability on the horizon, rational cooperation and collaboration are the only means to surmount this perilous threat.

2. A Highly Contagious, Zoonotic, RNA Virus

To embark on the journey of forecasting, the central question on everyone's lips pertains to the identity of Disease X. If we wish to be better equipped to prepare for the next disease, it is crucial to narrow down the scope of the enemy. I contend that viruses and bacteria are more likely to cause global pandemics owing to their high infectivity, ease of transmission, and lack of immunity. However, between the duos, bacteria lose their edge in the age of better sanitation and healthcare, especially when antibiotics have greatly reduced the mortality and morbidity associated with bacterial infections (Adedeji, 2016) (FastStats - life expectancy 2023). Admittedly, bacterial infections remain a significant cause of illness and death globally, as 7.7 million deaths around the world have been linked to bacterial infections (Ikuta et al., 2022), and antibiotic resistance is looming (Murray et al., 2022). There are still ways to mitigate those impacts (Monserrat-Martinez et al., 2019). Besides, resistant bacteria are unlikely to turn the world upside down, given the amount of attention they currently have.

By contrast, controlling viruses is a whole other ballgame. Unlike bacteria, which can often be treated with antibiotics, there are fewer effective antiviral medications available. Besides, viruses can mutate more rapidly than bacteria, which makes it harder to develop effective vaccines and treatments. The way viruses breed is even faster than bacteria. Studies have found that the growth of bacteria requires the synergy of many biochemical reactions (Maitra & Dill, 2014), while the way viruses do it is to invade and occupy the host cell to replicate themselves, which is apparently more efficient to increase its amount. Moreover, many viruses can be asymptomatic, which means people can be infected without even knowing it and unknowingly spread the virus to others. Myriad viruses can be spread through the air (Louten, 2023), which makes them more contagious than most bacteria that require close contact. A multitude of viruses can infect a variety of hosts, which can make it harder to control outbreaks. Therefore, the conclusion that viruses have outweighed bacteria as the more dangerous candidate X of our time, can be reached.

However, we are still fumbling in the dark when it comes to facing the most abundant biological entities on earth (Zablocki et al., 2016; Simmonds et al., 2017). The question remains: what makes some viruses exceptional as pathogen X?

Zoonotic viruses undoubtedly deserve top priority on the list. Historically, up to 75% of new or emerging infectious diseases and up to 60% of existing infectious diseases are thought to have zoonotic origins (Salyer et al., 2017), while a total of 56 zoonoses cause 2.7 million deaths and over 2.5 billion episodes of human sickness per year (CGIAR). Of recent note, the case of SARS-CoV-2, a virus linked to bats that host a bunch of notorious viruses, has caused the world to lose millions of lives and trillions of dollars (Ozili & Arun, 2022) (Estimated cumulative excess deaths during COVID, from the WHO). Zoonotic viruses have a significant impact on human life, based on previous knowledge, but are even more concerning as newly emerging zoonoses are becoming more frequent, and previously existing ones are spreading faster (CGIAR). Swine influenza is one such disease that is increasing among pigs, and animal trade is contributing to the spread of diseases across continents (Henritzi et al., 2020; Mena et al., 2016). Both facts and forecasts suggest that zoonoses deserve our attention, not to mention the intrinsic mechanisms of virus evolution, which demonstrate that viruses can and will spill over from animals to humans as a natural process of mutation and way of life (Grange et al., 2021).

Speaking of mutations, in the field of virology, one particular type of virus is particularly intriguing for its high mutation rate: the RNA virus. A study that examined over 500,000 samples and 74,000 animals identified the top 50 wildlife viruses with the highest potential for harm, and all but two of them were RNA viruses (Peck & Lauring, 2018). This comes as no surprise, with a rate up to a million times higher than their hosts, RNA viruses have the highest mutation rate of all species (Duffy, 2018). Generally speaking, such high mutation rates are due to the RNA-dependent RNA polymerases (RdRp), which exist in almost all RNA viruses, with the exception of retroviruses, and catalyze genome replication. However, this essential enzyme generally lacks proofreading activity when replicating genes, resulting in many errors, and contributing to the high mutation rate of RNA viruses (Drake, 1993).

One may wonder why RNA viruses have evolved to have such high mutation rates, especially considering that 20 to 40 percent of these changes are deleterious (Sanjuán, 2010). The trade-off of RNA viruses is particularly striking in demonstrating the determination of the species (Belshaw et al., 2008). Though favorable gene adaptations may be lost due to poor replication fidelity, these species choose to mutate as quickly as possible despite the possibility of self-destruction. It's important to think of viruses as a species, not as individuals, as mutation leads to genetic diversity and a greater potential for survival. As the Red Queen effect states, "it takes all the running viruses can do to keep in the same place. If they want to get somewhere else, they must run at least twice as fast as that!" Consequently, as long as the virus can move to its next host, speed is key.

The high infectiousness of a virus is a result of mutation; however, it remains unknown unless emergencies arise. The initial spread of COVID-19 in Wuhan serves as a prime example of this phenomenon, as an average R0 of 3.28 and a median of 2.79 resulted in a concerning spike in infections (Liu et al., 2020). However, the R0 is only one aspect of the challenge at hand. Most transmissions occur during the pre-symptomatic phase, which is further complicated by a highly variable incubation period that can extend beyond the peak of viral shedding (Goyal et al., 2021). Moreover, the virus spreads via respiratory transmission, enabling it to infect a larger number of people within equivalent physical contact networks, thanks to aerosolization (Goyal et al., 2021). Additionally, the virus requires a minimum viral dose to be delivered to a vulnerable site in a susceptible host (Meyerowitz et al., 2021), which relies on a specific affinity between the virus and host receptor that can be difficult to predict. While zoonotic transmission may bring viruses under our spotlight, the specific mode of transmission can often appear unexpectedly as a “black swan event”. This uncertain nature of the virus is disquieting, and a combination of viral, host, and environmental characteristics can complicate outbreak management. Although zoonotic diseases and genetics may aid in identifying the pathogen, it is ultimately the agnostic nature of infectiousness that necessitates constant vigilance and preparedness to prevent the spread of disease.

3. Preference for Emergence

Zoonotic RNA viruses have emerged as a formidable threat to human health, but the question of where the next outbreak of Disease X will occur remains shrouded in mystery. Fear not, though, for three important factors—high human density, extreme biodiversity degeneration, and limited medical resources—may assist in locating the Disease X and indicate methods for preparing in advance.

Population density is one of the critical factors in predicting the emergence of Disease X. The correlation between human population growth and infectious disease outbreaks has become increasingly evident in recent times (Baker et al., 2021). The surge in population numbers has outstripped the planet's capacity to support us, leading to a complex web of interrelated factors that elevate the risk of disease outbreaks. Meanwhile, encroachment of urban areas into wildlife habitats and the resulting increase in human-wildlife interactions have contributed to the spread of zoonotic diseases (Jones et al., 2013; Allen et al., 2017). Additionally, crowded urban areas increase the likelihood of person-to-person transmission, as pathogens are rapidly transmitted to densely populated areas where outbreaks are more likely to occur. According to a recent study published in Nature, human population density is an independent predictor of emerging infectious diseases (Jones et al., 2008). Identifying the most densely populated areas and developing response plans is a practical way to prepare for Disease X. Therefore, as we grapple with the unknown, prioritizing population parameters is crucial to ensuring global health and well-being.

Areas with high biodiversity and irregular exposure to wild animals, particularly in tropical regions, create an optimal environment for viral transmission (Jones et al., 2008; Constable, 2022). In such areas, viruses proliferate, and human intrusion into wildlife habitats increases the risk of contracting zoonotic diseases (Plowright et al., 2017). In fact, overdevelopment and habitat encroachment are causing bats to shed more viruses, raising the risk of spillover (Constable, 2022). Even seemingly harmless animals can cause trouble under extreme conditions, as evidenced by the outbreak of MERS in Africa, where locals rely on camels to survive the worsening drought and habitually consume raw camel milk, which can spread disease (Jacob Kushner in Marsabit, 2022). As the ecological environment continues to deteriorate, the likelihood of encountering unknown and uncharted aspects of the natural world increases (Macpherson, 2005). Given these circumstances, prioritizing areas with deteriorating biodiversity is a wise and necessary move.

The final indicator is medical resources. In areas with insufficient medical resources, particularly those with inadequate sanitation and healthcare systems, infectious diseases can run rampant, threatening the health and lives of the population. The World Health Organization (WHO) warns that poor sanitation can lead to a range of infectious diseases, including typhoid, cholera, dysentery, intestinal worm infections, and polio (Sanitation, 2022). However, this is just the tip of the iceberg. The scarcity of medical resources impedes every step of controlling infectious diseases, from early and ongoing surveillance to patient isolation and treatment. In the documentary film Virus Hunters, the outbreak of Ebola ravaged West Africa for months, largely undetected by local governments ill-equipped to handle this particular virus. With inadequate public health infrastructure, hospitals were quickly overwhelmed, leaving "those who care for the sick and prepare the dead for burials especially vulnerable to infection" (Pulley, 2020). One of the biggest tragedies of the Ebola outbreak is that it "spread through love," as families cared for and comforted their sick relatives, unwittingly increasing the likelihood of transmission. This is a powerful reminder that underfunded and understaffed medical facilities struggle to provide appropriate care to infected individuals and increase the likelihood of disease transmission.

4. Mitigation of Impacts

As we continue our search for answers, we have begun to narrow down the potential origins and locations of Disease X. However, certainty eludes us, and so we must prepare prudently with all our might against an unknown pathogen. Hopefully, we have a range of tools at our disposal, including disease surveillance, vaccination, and therapeutics. While each of these approaches presents its own set of challenges, we can tip the scale in favor of success by pursuing a broad-spectrum strategy, improving deployment, and fostering global cooperation. With these measures in place, we stand a much better chance of combating Disease X effectively.

4.1. Surveillance System.

Disease surveillance plays a crucial role in detecting and responding to emerging infectious diseases. With advancements in genomic sequencing, this field has been revolutionized, enabling us to better treat and prevent the forthcoming Disease X. The use of metagenomics, despite being a novel study, has allowed us to examine genetic material from entire microbial communities, offering valuable insights into the diversity and evolution of potential pathogens that may cause pandemics. Additionally, genomic sequencing of individual pathogens has proven to be an indispensable tool in disease surveillance. For example, during the Ebola outbreak in Congo, genomic sequencing helped identify the virus's origin in a specific bat species, which was critical in preventing further spread of the disease (Virus Hunters, 2022).

While effective surveillance of Disease X requires more than just technological advancements, innovative frameworks are emerging to help protect the world against the threat of pandemics. One example is the Global Virome Project, which aims to detect and identify zoonotic viral threats to human health and food security (Our goals). In Cambodia, researchers have launched a program to track the spread of the Nipah virus, using GPS tracking programs to gather information on the movement of disease-carrying animals (Constable, 2022). Additionally, a wider spatial risk map is being developed to provide a warning system for communities and health officials. This map will link information on possum abundance, bacterial quantities, and mosquito levels to offer comprehensive information on disease risk (Kushner, 2022).

However, it is worth noting that some impoverished nations may lack the necessary resources and laboratory capacity to detect and prevent outbreaks of human and zoonotic diseases. To address this, organizations such as the PREDICT program are researching animal viruses in specific hotspots of animal-human interaction, like the Amazon Basin, South and Southeast Asia, and the Congo Basin, to mitigate the risk of pandemics (Predict (USAID) 2023). Such efforts to bolster disease surveillance are crucial in improving the response to emerging diseases and preventing future pandemics.

4.2. Vaccination and Therapeutics.

Vaccines help prevent Disease X, while drugs aid in its treatment. Multiple vaccines and therapies have been developed in the case of the previous COVID-19 pandemic, but significant challenges remain (COVID-19 Vaccine Tracker and Landscape) (Zimmer et al., 2020). For instance, the initial Pfizer mRNA vaccine requires storage in −70 °C ultra-cold freezers, which poses a great challenge in distribution and administration. Another COVID-19 vaccine has been found to cause reactogenicity in response to Ad5-nCoV (CanSino Biologics) vaccination in individuals with and without previous SARS-CoV-2 infection (Hernández-Bello et al., 2021). Due to the high mutation rate of RNA viruses, human immunity appears to wane, as antibody levels decrease with time. However, research has shown that memory B cells take up the role of long-term immunity in vaccine protection. While memory B cells exhibit clonal turnover and continue to evolve in response to the virus, there is currently no method to examine the nature and quality of the memory B cells that would be called upon to produce antibodies upon re-infection (Gaebler et al., 2020). The truth is, knowledge, in the face of an unknown virus and the human body itself, is forever scarce. But what we have learned from COVID-19 and the everlasting battle against infectious diseases is that a broad-spectrum approach is necessary.

Developing broad-spectrum vaccines and therapies can be a promising means of treating an unknown disease. A brief introduction of how a broad-spectrum approach is designed would be helpful to elaborate on its effect. Pan-vaccines may target at least two different routes: one is the most conservative region shared by most variants, and the other is RBDs of different variants, which join as heterologous oligomers to cross-link antibodies and achieve broad-spectrum protection (Li et al., 2021). Pan-therapy may also be possible due to viral polymerase promiscuity (Majerová & Konvalinka, 2022). In other words, though viruses exist in abundant forms with different life cycles, there are similarities among close species. Single-stranded RNA viruses, for example, do not show significant differences in RdRP, which gives us an opportunity to develop broad-spectrum drugs. If those broad-spectrum technologies work well, we might really be able to nip the pandemic in the bud, just like we did to bacteria.

Besides the pan-approach of designing both vaccines and therapies, there are also broad-spectrum technologies and platforms (Taylor, 2007), which comprise standardized, reproducible manufacturing processes that can be adapted to produce vaccines and drugs against different pathogens (Gouglas et al., 2019), such as the “plug-and-play” platform, allowing us “to create countermeasures at speed” (World Health Organization Fears 'Disease X' could cause a global pandemic, 2018). These platforms are even less pathogen-specific, which gives us the possibility to deploy them at the moment.

4.3. Deployment and Cooperation.

In addition to technological innovations, there are also innovations needed in the deployment of strategies, which require coordinated efforts across nations and sectors, supported by funding, global organizations, and the general public.

Funding is a critical aspect of developing countermeasures against Disease X, which inherently entails risk and cost. A new entity, the Coalition for Epidemic Preparedness Innovations (CEPI), was set up in 2016 to stimulate, finance, and coordinate the development of vaccines against epidemic infectious diseases, especially in cases where market incentives alone are insufficient. In September 2019, CEPI established 16 crucial partnerships that facilitated the rapid development and manufacture of vaccine candidates, including investigational stockpiles for large-scale efficacy trials during outbreaks (Gouglas et al., 2019). Without such partnerships, large-scale vaccine efficacy studies would be virtually impossible due to the sporadic emergence of epidemic infectious diseases (Gouglas et al., 2018).

Another crucial aspect of deploying medical strategies is global collaboration, with regional and sub-regional institutions playing vital roles in regulatory harmonization, reporting standards, information sharing, and sharing key public health assets (Uribe et al., 2021). To ensure timely and equitable access to medical resources, joint procurement mechanisms like COVAX and the African Vaccine Acquisition Trust Fund (AVAT) are necessary (COVAX: The forecast for vaccine supply 2023) (AVATT Archives). Also, addressing vulnerabilities associated with the breakdown of global supply chains is important. For example, not every country needs its own vaccine manufacturing capacity, but we need to ensure that there is sufficient production capacity in developing countries that can be quickly scaled up, which requires a global effort to deploy.

While international cooperation may sound grand and lofty, the implementation needs to get down to earth. One key area that needs attention is the gap between medical professionals' knowledge and the public's understanding. Lack of awareness can lead to conspiracy theories and poor compliance, as seen during the COVID-19 pandemic. To address this, we need education, we need to focus on real issues facing people, such as the overwhelming burden of healthcare, to build trust and bridge the gap, and we need to be user-friendly, like with easily accessible apps that help identify "non-notifiable" diseases (Constable, 2022) and mobile data collection systems that proved successful in detecting anthrax outbreaks among buffalo in Kenya (Jacob Kushner, 2022). By integrating people in public health efforts, we can create powerful and effective tools to combat Disease X.

5. Conclusion

The emergence of a highly infectious Disease X is not a matter of if, but when. While we may not know the specifics, we narrow down some highly potential characteristics of disease X as being a highly contagious zoonotic RNA virus and circle the areas with high population density, biodiversity deterioration, and poor sanitation as locations of a potential health threat. While the emergence of Disease X may seem daunting, we have the knowledge and tools to prepare for the battle against it, which requires a multi-pronged approach, and significant progress has been made in disease surveillance, vaccines, and therapeutics. The deployment of strategies requires coordinated efforts across nations and sectors supported by funding, global organizations, and the general public. However, since knowledge of an unknown virus and the human body itself remains scarce, we need to prudently prepare for what we can, while continuing to pursue what we can do better, thus mitigating the impact of the next Disease X.

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