Lessons for the next pandemic from COVID-19 and other emerging viral zoonoses

Graham Casey MSc[†]

Abstract

SARS-CoV-2 is a novel coronavirus that emerged rapidly and caused devastating effects worldwide. Understanding principles of virus emergence is necessary to adequately prepare for future pandemics. It is also important to understand and appreciate public health and human behavioural responses to outbreaks. Examining specific emerging zoonotic viruses can provide insight into general trends in viral emergence. In this narrative review, three emerging viruses and one potentially emerging human virus are discussed with comparisons to the ongoing SARS-CoV-2 pandemic. Their emergence is framed within a five-stage model for emerging infectious diseases described previously. Ebola virus, Nipah virus, monkeypox virus, and canine distemper virus are used as examples of emerging and potentially emerging viral zoonoses. These viruses are described in order to develop a better understanding of the breadth of existing emerging viruses, the means by which they emerge into human populations, and of how human behaviour shapes the course of their emergence.

Keywords: viral emergence, zoonoses, ebolavirus, henipaviruses, poxviruses

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Introduction

The current COVID-19 pandemic shows what damage an emerging virus can cause. SARS-CoV-2 is currently hypothesized to have been introduced into humans from an animal source (likely bats) in late 2019. The first cases appeared to cluster in Wuhan, China but quickly spread worldwide.[1–3] Along with questions about the origins of SARS-CoV-2 come questions about what other viruses circulate in animals ready for the right conditions to spark the next pandemic.

There exists a five-stage model for emerging infectious diseases initially described by Wolfe et al.[4] with important modifications from Lloyd-Smith et al.[5] It describes the stages of emergence of a zoonotic pathogen from an exclusively animal pathogen (stage I) to an exclusively human pathogen (stage V), with diseases that are transmitted from animals to humans (referred to as zoonoses) representing stages II to IV (Table 1). In this narrative review, a selection of emerging viral pathogens will be discussed using the framework of this five-stage model. Discussion of these emerging viral pathogens will be used to illustrate factors that modulate the progression of a virus from causing an animal disease to a disease with pandemic potential. Connections will then be made to the story of SARS-CoV-2.

There are many emerging viruses with important aspects worth discussing, but only a few will be discussed in this review. Ebola virus is a stage IV pathogen that provides a strong example of the transition from causing an animal viral disease to a human viral disease. It also demonstrates how human behaviour, largely motivated by fear and distrust, shapes pandemics. The two strains of Nipah virus demonstrate the distinction between a stage II and stage III emerging virus. They also show how the context of the emergence of a virus is influenced by human-animal interfaces, politics, and cultural practices. Disease X is discussed to highlight that the next pandemic could be caused by a virus that is unexpected or undiscovered. The two viruses chosen to represent Disease X (monkeypox virus and canine distemper virus) were chosen for their relevance to the discussion of the "species barrier," consequences of viruses with broad host ranges, and difficulties predicting the cause of the next pandemic.

Ebola virus

Ebolavirus is a genus in the family *Filoviridae* containing several viruses including Ebola virus (EBOV, species *Zaire ebolavirus*), the causative agent of Ebola virus disease (EVD). EBOV was first discovered in the

*Correspondence to: caseyg@myumanitoba.ca
[†]Max Rady College of Medicine, University of Manitoba

Democratic Republic of the Congo (DRC), formerly Zaire, in 1976.[6] To date, there have been 21 known outbreaks of EVD.[7–9] The largest outbreak was the 2013-2016 West Africa Ebola epidemic, with 28 646 suspected cases and 11 310 deaths.[6] The end of the epidemic in 2016 was not the end of EBOV. There have been seven more outbreaks of EVD since, including two EVD outbreaks in 2021 in the DRC and Guinea.[8]

EBOV is a zoonotic virus. Initially regarded as a hemorrhagic fever virus, this definition was reconsidered when the predominant manifestation of EVD in the West African EVD epidemic was severe gastroenteritis and multiorgan failure, with rare cases of bleeding described.[6] The animal reservoir is not definitively known but is suspected to be African fruit bats.[6] Historically, each outbreak appeared to involve contact with tissues or secretion of infected or dead wildlife.[6] EBOV is considered to be highly infectious, requiring small doses of virus to cause disease.[10,11] The human-to-human transmission occurs via direct contact with bodily fluids of infected individuals (including blood, vomitus, diarrhea, urine, saliva, breast milk, semen, and potentially sweat). Individuals in contact with infectious fluids can become infected if the virus contacts oral, conjunctival, or respiratory mucosa, or breaks in the skin.[10,11] Recently, more attention is being given to the long-term persistence of EBOV in the semen of EVD survivors and sexual transmission of EBOV.[12]

During the West African EVD epidemic, it became clear that EBOV should be considered a stage IV emerging pathogen. While it is suspected that the epidemic still started with an animal-to-human transmission event, EBOV was capable of sustained secondary transmission between humans.[13,14] Concerningly, the three most recent outbreaks (DRC 2020, Guinea 2021, and DRC 2021) are thought to have originated from long-term persistence of EBOV in EVD survivors from previous outbreaks rather than from contact with an animal source.[8,12,15] This indicates a potential mechanism by which EBOV could circulate in human populations without first being introduced by animals. Such a mechanism stands in contrast to previous EVD outbreaks wherein human-to-human transmission occurred but outbreaks were thought to originate from animal sources and secondary transmission was apparently self-limited (i.e. a stage III pathogen).[6]

In the West African EVD epidemic, significant EBOV transmission from the still-infectious bodies of EVD victims occurred during funerary and burial rites. When this was determined, the World Health Organization (WHO) made recommendations that heavily restricted traditional burial practices.[16] Rituals varied, but commonly involved washing and spending time with the body.[16,17] The WHO's recommendations were traumatizing to many cultures and were met with resistance due to the significant alteration to their core way of life and the distressing imposition by a foreign authority on traditional cultural practices.[16,17]

Public health responses to global threats must take care to be culturally sensitive. Otherwise, they may be met with significant resistance. This has been seen locally during the SARS-CoV-2 pandemic in the vocal opposition to pandemic restrictions on religious gatherings in Manitoba. For example, these restrictions were met with noncompliance in the form of the Steinbach protests.[18,19] The effects of culture on health behaviours in a pandemic can be seen on a broader scale in the differential adherence to public health policies according to political ideology[20] and in the differences in the policies themselves.[21,22]

The impositions on local culture in the West African EVD epidemic contributed to the already substantial fear permeating the outbreak. Descriptions of EVD were terrifying. The alien-like personal protective equipment, healthcare workers falling sick, and stories of loved ones disappearing into Ebola treatment units (ETUs) only to be returned dead all contributed to the spread of fear. This fear fueled the spread of EBOV.[17] People hid when sick or insisted on caring for loved ones at home. They fled from EVD-stricken areas, bringing virus with them. Contingents of healthcare workers stepped down from their roles in the face of EVD.[17]

In the Kivu 2018 outbreak, such fear and foreign imposition coalesced into violence. Wells et al.[23] describe "rumors about foreigners experimenting on locals, taking organs, and filling the bodies with concrete and Ebola being a fabrication" among locals in the Katwa health region that preceded a violent riot at a nearby ETU.[23] An important lesson from the EVD outbreak is the impact that fear can have on the evolution of an outbreak. Similar examples from the ongoing SARS-CoV-2 pandemic have been observed. These include the avoidance of necessary healthcare for fear of acquiring COVID-19[24] as well as the psychological toll on healthcare workers,[25] patients,[26] and public following isolation guidelines.[27]

Nipah virus

Nipah virus (NiV) is an emerging zoonotic paramyxovirus in the genus *Henipavirus* consisting of 2 strains: NiV-Malaysia (NiV-M) and NiV-Bangladesh (NiV-B). They are named after the locations where they first emerged. Both NiV-M and NiV-B cause a high-mortality severe encephalitis and respiratory syndrome in infected humans.[28,29] The reservoir host for both strains of NiV is fruit bat genus *Pteropus*.[30] NiV-M and NiV-B have been largely epidemiologically distinct, and so they will be discussed separately from each other.

Nipah-Malaysia

The first outbreak of NiV in 1998-1999 was the only outbreak of NiV-M. It resulted from the transmission of NiV-M from Pteropid bats to pigs, and then from infected pigs to the humans.[31] Unlike in humans, NiV-M was easily transmitted between pigs, had a low case-fatality rate, and often produced no or mild clinical signs.[31] Pigs functioned as excellent amplifying hosts for NiV-M, greatly expanding the interface for expo-

sure in humans. NiV-M was transmitted from infected pigs to humans mainly through close contact during routine pig farming procedures (such as piglet processing, assisting in birthing, or preparation for slaughter). This exposed people working with live pigs to aerosolized droplets from respiratory and oronasal secretions of the pigs.[32–35] In this outbreak, all human cases of the disease were traced to infected pigs. There was no definitive proof of human-to-human transmission, making NiV-M a stage II zoonosis.[36]

The emergence of NiV-M was a result of co-agricultural practices that kept mango orchards and pig herds on the same land with no barrier between them. NiV-M-carrying Pteropid bats fed from fruit trees overhanging pigsties. They occasionally dropped virus-contaminated fruit (with bat urine or saliva) into the sties for pigs to sniff, consume, and become infected.[37–40] Evidence suggests that the emergence of NiV-M into pigs had been ongoing for several years. The outbreak in 1998-1999 was made possible by the pattern of repeated bat-to-pig transmission over time.[38,41] Each NiV-M introduction into pigs caused mini-epidemics in pig herds that quickly spread through the population. Agricultural practices of keeping sows long-term while selling young pigs early prevented herds from developing total immunity to NiV-M infection by ensuring a rapid turnover of susceptible hosts. Paradoxically, the state of partial immunity to NiV-M allowed epidemics to burn for longer and spread more widely than in a wholly NiV-naïve population. This occurred until NiV-M ultimately exceeded a threshold in pig herds that resulted in spillover into humans.[38,41] Prevention of future similar outbreaks requires rigorous surveillance as well as rethinking how to avoid agricultural practices that increase the risk of exposure to, and adaptation of, novel viruses.

Many human social and political factors also influenced the course of the NiV-M outbreak. Malaysian pig farmers engaged in the practice of "fire sales", or panic selling in the face of a disease outbreak. This contributed to the spread of NiV-M infections throughout Malaysia and into Singapore.[38] The outbreak was at first mistaken for an outbreak of Japanese encephalitis virus (a vaccine-preventable, mosquito-borne virus). This resulted in the Malaysian government ineffectively responding with JEV vaccinations and anti-mosquito fogging.[42] Even short delays in the recognition of an emerging pathogen can have devastating consequences. Indeed, there are many accusations of various countries' slow, surprised response to SARS-CoV-2[43] and of poor information-sharing early in the outbreak.[44–48] The 1998-1999 NiV-M outbreak was eventually controlled by the culling of over a million pigs in Malaysia.[32] No confirmed human infections of NiV-M have been observed since.

Nipah-Bangladesh

All subsequent NiV outbreaks have involved NiV-B, occurred in Bangladesh or India, and have been initiated by direct transmission of the virus from Pteropid bats to people. This cross-species transmission of NiV-B has commonly been mediated by human consumption of raw date palm sap, which is harvested from open containers hanging in trees available to bats.[29,36] Multiple small outbreaks of NiV-B have occurred since 2001 in a similar pattern to the outbreaks of EBOV between its 1976 discovery and the 2013-2016 West Africa outbreak. This pattern is referred to as stuttering transmission, describing the outbreak pattern of an emerging virus that is capable of self-limited (i.e. not indefinite) human-to-human transmission. Stuttering transmission can represent an important phase in the adaptation of a virus into a new host.[49]

Like what was observed with EBOV, some cultural practices in Bangladesh contributed to NiV-B outbreaks. Boiling date palm sap before consumption could have prevented many index infections. However, consuming raw date palm sap is important to Bengali culture and the risk of infection is low overall. As such, this behaviour is difficult to modify.[50] Striking a balance between safe, long-term behaviour change versus disrupting culturally-important behaviours is a complicated task in global health. Discussion with affected communities is critical in order to develop effective interventions. For NiV-B, simply using bamboo skirts on date palm sap containers can effectively reduce bat contamination of sap while requiring little behaviour change or invasive demands.[51–53] For SARS-CoV-2, an analogy may be made to calls to shut down wet markets in China.[54–56] Although the calls appear as a promising pandemic prevention strategy, they oversimplify the complex issue of intersecting cultural traditions and socioeconomic forces. An approach to emerging infectious diseases must account for these complexities. Obtaining cooperation requires working with affected parties as opposed to dictating to them.[57,58]

NiV-B saw fewer instances of animal-to-human transmission than NiV-M. Unlike NiV-M, NiV-B outbreaks have involved multiple instances of human-to-human transmission. This makes NiV-B a stage III zoonosis.[36,59] Human-to-human NiV-B transmission risk factors include close contact (e.g. touching a patient or their secretions, or being near them when they cough) and aerosolizing procedures in the absence of proper personal protective equipment.[36]

A cultural norm in Bangladeshi healthcare is for family members to provide significant hands-on care and close physical comfort to the sick, especially near the time of death.[60] In severe illness, family members are described as cradling their loved one's head in their laps, attempting to spoon-feed them, or hugging and kissing them.[36,60] Family in Bangladesh perform much of the hands-on care in-hospital.[60] Cruelly, transmission of NiV-B in this cultural context of compassionate care results in infection of people who are at the same time loved ones and healthcare providers. These cultural practices also contributed to some superspreading events where a single infected individual transmits the disease to an unusually high number of people. In one

case, an important religious figure was ill with NiV-B and transmitted the virus to 22 devotees who had come to perform ceremonial rites for him in his illness.[36] Superspreading has also been described for SARS-CoV-2 and may inform public health responses by targeting them towards certain behaviours.[61] Similar to what was seen with the 2013–2016 West Africa Ebola outbreak, cases of NiV-B have also been attributed to burial practices.[36,62] Pandemics force societies to address what they can sacrifice, such as conceptions of good healthcare or a good death. For the purposes of the current pandemic, healthcare bodies must therefore consider the number of people who have and will die alone in hospitals to prevent the spread of COVID-19.[63]

Disease X

The WHO's list of priority pathogens for research and development in emergency contexts has included "Disease X" since 2016.[64–66] Disease X refers to a pathogen that is not yet known but could have large impacts on human health. SARS-CoV-2 is a strong example of this. Including Disease X on the list of priority pathogens is important because the viruses of which we do not know outnumber the ones that we do know. Therefore, the next pandemic virus could easily be drawn from the vast pool of undiscovered virus species.[67–69] It is difficult to study or review viral pathogens that are unknown. Consequently, there is significant interest in determining exactly what changes in a virus may allow it to cross the species barrier, increase its virulence, or increase transmissibility.

Monkeypox virus

Monkeypox virus (MPXV) is a zoonotic virus in the genus *Orthopoxvirus* that is related to the now-eradicated variola virus (VARV), the causative agent of smallpox. MPXV causes a disease similar to smallpox that is not as deadly. Most cases occur in the DRC[70,71]. MPXV has been a growing concern since the cessation of routine smallpox vaccination, which historically provided some cross-protection to all orthopoxviruses.[70] Transmission of MPXV between humans occurs with relatively low efficiency and usually by the respiratory route. MPXV can also infect through mucosal surfaces and breaches in the skin.[72,73] The low-efficiency transmission makes MPXV a stage III emerging virus as it cannot sustain human-to-human transmission indefinitely.[70] Similar to NiV-B and early EBOV, MPXV appears to be in the stuttering transmission phase of emergence. Its transmission efficiency may also be increasing.[71,74,75] Vaccines against MPXV are being developed for use in the DRC to specifically prevent MPXV infections.[76] However, with an existing animal reservoir, it is unlikely that MPXV could be eradicated.

Despite its name, MPXV's natural reservoir is suspected to be an ecologically complex group of small terrestrial mammals prevalent in forest margins and peridomestic zones near human habitations. Monkeys, like humans, are incidentally infected.[75] MPXV's broad host range indicates it might be more tolerant to interspecific host variations and thus amenable to adaptation in humans.[77] While it is not true that all viruses with broad host ranges are dangerous to humans, many emerging viruses (including NiV, EBOV, and SARS-CoV-2) have broad host ranges.[78–80] Additionally, MPXV can infect monkeys, which may give it an advantage to emergence into humans. This is because it already infects a species that is (relatively) genetically similar.[71] Genetic relatedness of animal reservoir species is not a foolproof method of identifying emerging virus threats, but it can help narrow the field of likely animal sources of emerging viruses. For example, a paper published in January 2020 suggested that snakes might be the source of SARS-CoV-2.[81] This has since been discounted, but even in the uncertainty of the early COVID-19 pandemic, the vast species differences between humans and reptiles were a plausible reason to consider this hypothesis unlikely.[82]

Canine distemper virus

Another example of a candidate "Disease X" is canine distemper virus (CDV). CDV is a virus in the genus *Morbillivirus*, family *Paramyxoviridae*, which also contains measles virus (MeV; a stage V pathogen, only infecting humans). CDV has a broad host range including canines (the primary host), large cats, ferrets, seals, and Macaca primates. Transmission of CDV between animal hosts is thought to be by production and inhalation of infectious aerosols.[83] It is highly contagious in many hosts and in some it is highly lethal (with case fatality rate as high as 90%).[84,85] Currently, CDV is a stage I pathogen with no reported human cases. However, evidence has been found that circulating strains of CDV could be as little as one amino acid change away from efficient infection of human cells.[86,87]

Fortunately, similar to MPXV before smallpox eradication, CDV emergence into humans may currently be prevented by cross-protective immunity from MeV vaccinations.[88] Even without pre-existing heterologous immunity from MeV vaccines, there are far more barriers to interspecies transmission than just viral entry. It may therefore be presumptuous to offer that a single amino acid change on the CDV receptor is sufficient for transmission to and between humans.[89]

Nevertheless, there are many reasons for concern about a virus such as CDV. The broad host range of CDV suggests that it could quickly adapt to human hosts.[77] Humans have a large interface with CDV-susceptible animals, particularly domestic dogs.[85] Outbreaks of zoonotic viruses do not bode well for the affected humans or animals. The discovery that SARS-CoV-2 could infect cats resulted in public health recommendations for protecting both household pets and pet owners,[90] but these did not stop people from abandoning or killing housecats.[80,91,92] Zoonotic viruses affecting agricultural animals are usually controlled by

large culls,[32,93,94] as was recently demonstrated with SARS-CoV-2 and mink farms in the Netherlands and Denmark.[95,96] Such control methods come at a significant cost to the relevant economies and the psychological wellbeing of the farmers and cullers involved.[97–99] A virus with a broad host range is a threat to more than just human health.

Of course, CDV may never cause a human case. However, the above concerns about CDV have all been realized in some way by SARS-CoV-2 and other emerging viruses. What are the chances that CDV is the only virus that is a few mutations away from infecting humans? In contrast to the lengthy stuttering transmission phases of NiV-B and EBOV, SARS-CoV-2 has demonstrated that an unknown virus can emerge into a worldwide pandemic within months.

It is at the boundary of the unknown viruses – Disease X – where predictions become difficult.[100] Similar arguments to CDV could be made for any number of pathogens.[88,101] By attempting to identify exact viral agents, researchers are forced to select from the known viruses and fall prey to publication bias and the availability heuristic. There are many unknown viruses.[67–69] How do we protect ourselves from so much unknown?

Conclusions

There exists an unnerving task: to prepare for future pandemics without knowing what will cause them. A multifaceted approach is required. Research should focus on strategies for pandemic prevention and preparedness that can be broadly effective for classes of viruses. Clear communication of rigorous research between scientists, governments, public health offices, healthcare providers, and citizens is imperative. Social and public health strategies should focus on basic infection prevention and control strategies that are easily deployed, such as barrier precautions, masks, and hand hygiene. The interfaces between human populations, domestic animals, and wildlife should be carefully observed so that signs of emerging threats or spillover can be addressed. Environmental stewardship, responsible agriculture, and ethical interactions with wildlife should be practiced.

Human behaviour drives pandemics. Past outbreaks and epidemics can help us to understand human behaviour in the COVID-19 pandemic and hopefully to understand the rationale behind public and global health responses. The emergence of SARS-CoV-2 has afforded us our reluctant opportunity to reflect on a situation that less than two years ago was science fiction. How have I acted in this pandemic? What should I be doing to prevent or survive the next one? What are we ready and able to sacrifice? Hopefully, with all that has been learned up to and throughout the COVID-19 pandemic, the world is a small step farther away from the next one.

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