Praemonitus praemunitus: can we forecast and prepare for future viral disease outbreaks?

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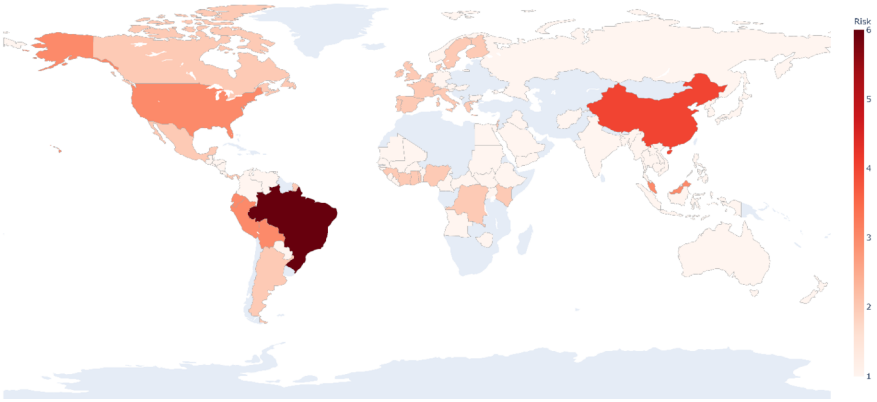

Featured Image: Visual representation of countries at risk for originating new viral outbreaks

Summary Sentence: While future viral outbreaks are unavoidable, we should be able to forecast the time and location of the outbreaks and minimize their potential impacts through consistently funded research in the fields of virology and antiviral drug discovery.

Keywords: viral outbreaks, epidemics, influenza, coronavirus, Mayaro, Oropouche.

Abstract

Understanding the origins of past and present viral epidemics is critical in preparing for future outbreaks. Many viruses, including SARS-CoV-2, have led to significant consequences not only due to their virulence, but also because we were unprepared for their emergence. Today, we face a harrowing, yet all too important challenge: to learn from large amounts of data accumulated from well-studied past pandemics and employ modern informatics and therapeutic development technologies, both to forecast future pandemics and help minimize their potential impacts. While acknowledging the complexity and difficulties associated with establishing reliable outbreak predictions, herein we provide a perspective on the regions of the world that are most likely to be impacted by future outbreaks. We specifically focus on viruses with epidemic potential that require attention from both the public and the scientific community to avoid becoming catastrophes like COVID-19. Based on our literature review, data analysis, and outbreak simulations, we posit that these future viral epidemics are unavoidable, but their societal impacts can be minimized. As a critical component of assuring our preparedness for combatting future pandemics, we strongly emphasize the importance of consistent funding of the fields of virology and antiviral drug discovery research.

Introduction

There have always been predictions about the day the world will end; some called it doomsday, others Armageddon, Ragnarok, or "The Rapture" (Sylvia Browne 2008). Predictions for this date have ranged from ancient times to millions of years in the future, as can be seen in writings from ancient Roman theology, religious staples such as the *Bible*(Sylvia Browne 2008), novels like *The Time Machine* (Wells 1895), and pseudo-sciences like modern astrology (Newman 2010). With the world still battling SARS-CoV-2 in 2022, and despite vaccine development and distribution at an unprecedented speed (Excler *et al.* 2021), the thought of the next pandemic is as frightening as the paradigm of "the end of the world as we know it" (Berry *et al.* 1987). In the face of the current burden that SARS-CoV-2 has caused, it is still essential to recognize what modern history has taught us. In this perspective, we attempt to review, systematize, and summarize methodologies and outcomes of the viral outbreak predictions that have appeared in the literature over the years. On the basis of this analysis, we further attempt to identify regions of the world where the next outbreaks are more likely to occur and summarize developments that can help us prepare for such outbreaks.

Throughout the twentieth century, several strains of deadly influenza hit the world. The most severe, the 1918 influenza (better known as Spanish flu or the Great Influenza), infected 500 million people and killed an estimated 20-50 million people worldwide (Centers for Disease Control and Prevention (CDC) 2019a). In the last forty years, several viruses have caused global epidemics that have substantially affected humankind including (but not limited to) Human Immunodeficiency Virus (HIV), Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), Middle East Respiratory Syndrome coronavirus (MERS-CoV), Ebola virus, Zika virus, the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) (Morse *et al.* 2012) and the currently emerging concerns about the monkeypox virus outbreak, lack of treatments, and its continued spread (Centers for Disease Control and Prevention (CDC) 2022a). Factors like expanding mosquito-borne viral diseases and climate change (Reperant and Osterhaus 2017) contribute to sincere concerns about what virus is to come next, and whether we are prepared to prevent future viral outbreaks (Gates 2020). Some groups attribute the increase in viral epidemics to human population growth (Bloom, Black and Rappuoli 2017; Baker *et al.* 2021; Spernovasilis *et al.* 2021). It has been suggested that there is a 22-28% chance of a COVID-19 scale viral outbreak again in the next 10 years, and a 47-57% chance of such an outbreak over the next 25 years (Oppenheim 2021). These estimates should warrant a drastic surge in antiviral drug discovery and vaccine development research to alleviate the negative impact of future pandemics.

Virologists have always been concerned about the next epidemic. For example, in 1970, annual global rates of the 1968 Hong Kong influenza were being monitored by many groups (Gill *et al.* 1971; Mandin*et al.* 1971; Salim 1971; Gill and Murphy 1972; Jackson, Vynnycky and Mangtani 2010) and, in 1999, it was suggested that the next influenza outbreak would be a pandemic (Keavey 1999). In 1997, Andrick*et al* .

(Andrick *et al.* 1997) discussed the prediction of the viral outbreaks as it relates to climate change and, in *The Coming Plague* , Laurie Garrett discussed the epidemiological past of many viruses and their possible impact on the future of modern society (Garrett 1994). More recent projects such as the Global Virome Project (GVP) (Carroll *et al.* 2018) and PREDICT (PREDICT 2009) aimed to analyze all available public health data on every possible zoonotic virus in the hopes of preparing for the next outbreak. The PREDICT project uncovered nearly 1,000 novel viruses but, ironically, was shut down just prior to the emergence of the SARS-CoV-2 pandemic (Global Biodefense Staff 2020).

Understanding possible causal factors behind past and present viral infections is crucial to prepare for future epidemics. Tools such as HealthMap (https://www.healthmap.org/en/), which aggregates all viable resources to locate small-scale and unnoticed outbreaks, are essential and developing pre-emptive strategies to deal with new viruses is imperative to mitigate future outbreaks (Myers *et al.* 2000; Boston's Children Hospital researchers 2006). Recently, the Director-General of the World Health Organization's reinforced that humankind must be better prepared for the next pandemic, since outbreaks are "facts of life," and called on countries to invest more in public health (Reuters Staff 2020).

Below, we consider the factors responsible for the emergence, growth, and eradication of both current and previous viruses including SARS-CoV, MERS-CoV, Ebola virus, Zika virus, SARS-CoV-2, Dengue virus, Mayaro virus, Lassa virus, noroviruses, influenza, Nipah virus, hantaviruses, Oropouche virus, and Marburg virus (De Clercq and Li 2016). We collate information about human viral pathogens with epidemic potential and provide recommendations for how to prevent these viruses from realizing said potential, as well as a perspective on the next outbreaks and regions of the world that might be primarily affected by them. Establishing the value and accuracy of outbreak predictions is crucial to solicit the minimal impact of novel outbreaks given the minimal available therapeutics (Bobrowski *et al.* 2020). Indeed, currently, very few approved antiviral drugs are available to treat diseases caused by the viruses reviewed herein: a handful of drugs to treat influenza, a repurposed FDA-approved drug and EUA drugs against SARS-CoV-2, and one antibody treatment against Ebola (Centers for Disease Control and Prevention (CDC) 2021a, 2021b; U.S. Food & Drug Administration (FDA) 2022). Although current approaches cannot forecast the exact time and place of the new outbreak, based on a systematic literature review, data analysis, and outbreak simulations we surmise that the next viral epidemics are unavoidable. We summarize the existing and potential treatments, including both molecular therapeutics and vaccines, and strongly emphasize the importance of continued funding of both virology and antiviral drug discovery research as critical means to minimize the burden of future pandemics on mankind.

A tale of the outbreaks

In the discussion that follows, we will reference both the first event and the occurrence of disease cases above average expectancy as an "outbreak." However, as we analyze the outbreak forecasts retrospectively, it is crucial to understand what event(-s) are qualified as an outbreak and what are not. For example, the first case of MERS-CoV in the U.S. occurred on May 1, 2014 (months after it was rampant in the Middle East in March 2014), but the *outbreak* did not begin until May 16, 2014 (Bialek *et al.* 2014). For this reason, we shall clarify the meaning and use of the term '*outbreak.*' According to the CDC, an *epidemic* refers to "an increase, often sudden, in the number of cases of a disease above what is normally expected in that population in that area", but an*outbreak* is typically considered an epidemic in a geographically confined area (Centers for Disease Control and Prevention (CDC) 2019b). This definition, however, is subjective and depends entirely on the severity of the disease, location, frequency, and spread of the virus. Therefore, the term "outbreak" may be frequently used inappropriately or out of context by many of the sources referenced in this review. In some situations, a single case can constitute an outbreak, while in others, thousands of cases should be reported to constitute an outbreak (Professionals and Infection Control and Epidemiology 2014). Discrepancies like this were evident in our literature search as well, where some viruses had multiple models, some had simulations, and some had no more than observations from past

outbreaks. Several groups have tried to develop outbreak prediction models, albeit with limited success. In **Table 1** , the dates and information associated with these predictions are charted. Most of these models proved to be inaccurate or were reported retrospectively. However, some of these efforts can still be useful as warnings and/or observations. For instance, the epidemiological surveillance network monitoring of Ebola in the Congo (Rouquet *et al.* 2005; Asher 2018) and norovirus in the United States (Wang and Deng 2016) resulted in accurate predictions of the outbreak occurrences. These networks' successes were largely due to their foundations in infection tracing, described below when we discuss the Ebola virus and norovirus, respectively. Given the last-minute circumstances of the MERS prediction (Bialek *et al.*2014), this aligns more to an alert than a prediction, and both the Zika (Counotte *et al.* 2019) and Lassa fever (Fichet-Calvet and Rogers 2009) predictions were too far removed to determine their accuracy. In all, there is an acute difficulty in accurately assessing when a new outbreak will appear. Furthermore, in some cases (such as with Ebola), even the forewarning was not enough to prevent the outbreak. Factors such as host-vector transmissibility can be difficult to model due to the vastness of the global virome (Albery *et al.* 2021), and many others are too dependent on individual viral or environmental features. In **Table 2** , we describe the molecular biology behind each of the viruses herein, and in the following sections we provide detailed discussions of their outbreak risk based on data and literature analysis. Because different past outbreaks received varying levels of attention and scrutiny, the depth and amount of information discussed below will be different for each virus, with the most elaborate discussion being of the current COVID-19 pandemics.

Table 1. Summary of predicted outbreaks .

Disease	**Predicted date of the outbreak**	**Actual date of the outbreak**	**Outbreak Locatio**
Ebola	December 7, 2002	December 25, 2002	Kelle, Congo
Ebola	June 2003	November 2003	Mbanza, Congo
MERS	May 2014	April 23, 2014	United States
Norovirus gastroenteritis	December 29, 2013	December 26, 2013-January 9, 2014	United States
Lassa fever	March 2009	January 1, 2017- January 23, 2018	Liberia (Bong, Gra
Zika fever	January 1, 2035	-	Nicaragua

* If the date when the prediction was made was not available, the date of publication was assumed to be the date of prediction. Lines shaded in light green are considered accurate predictions, orange are alerts, red are inaccurate predictions (due to significantly inaccurate location or time), and purple are predictions of future events.

Table 2. Molecular biology, disease characteristics, and timelines of virus discovery and outbreak.

Virus	**Genome Organization**
SARS-CoV-2	Spherical, enveloped virus with single-strand, linear, positive-sense RNA genome (˜29.9 Kb) (Naqvi *et a*
SARS-CoV	Spherical, enveloped virus with single-strand, positive-sense RNA genome (˜29.7 Kb) (Xu *et al.* 2003)
MERS-CoV	Spherical, enveloped virus with single-strand, positive-sense RNA genome (˜29.9 Kb) (Chu *et al.* 2014)
Ebola virus	Filamentous, enveloped virus with single-strand, negative-sense RNA genome (˜19.0 Kb) (Bharat *et al.*
Zika virus	Spherical, enveloped virus with single-strand, positive-sense RNA genome (˜10.8 Kb) (Wang *et al.* 2017
Dengue virus	Icosohedral, enveloped virus with single-strand, positive-sense RNA genome (˜10.7 Kb) (Kuhn *et al.* 200
Mayaro virus	Icosohedral, enveloped virus with single-strand, positive-sense RNA genome (˜10.7 Kb) (Ribeiro-Filho *e*
Lassa virus	Round, enveloped virus with two single-strand, ambisense RNA segments (˜3.4 Kb [S] & ˜7.0 Kb [L]) (F
Norovirus	Icosohedral, non-enveloped virus with single-strand, positive-sense RNA genome (˜7.5 Kb) (Chan, Kwan
Influenza virus	Filamentous or spherical, enveloped virus with eight (influenza A and B) or seven (influenza C) single-st
Nipah virus	Spherical, enveloped virus with single-strand, linear, negative-sense RNA genome (˜18.2Kb) (Eaton *et a*
Hanta virus	Spherical, enveloped virus with three single-strand, negative-sense RNA segments (˜1.8-2.1, 3.7-3.8, 6.5-6
Oropouche virus	Spherical, enveloped virus with three single-strand, negative-sense RNA segments (˜6.9, 4.4, 1.0 Kb segn
Marburg virus	Filamentous, enveloped virus with single-strand, negative-sense RNA genome (˜19.1 Kb) (Fujita-Fujihar

Major viral outbreaks

Coronaviruses

SARS-CoV-2 (2019 - present)

History . Despite the recent novelty of coronaviruses as known to the general population, five to six coronaviruses have emerged and have circulated within the human population over the last 20 years (Stasio 2020). Until 2002, human coronaviruses were considered mild and responsible for illnesses like the common cold (Ye *et al.* 2020). SARS-CoV then surfaced in China that same year and spread to several other countries within a few months (Gralinski and Baric 2015). Studies conducted at food markets in southern China discovered that almost half of wild animal traders were seropositive for SARS-CoV during the 2002 outbreak (Kahn and McIntosh 2005). Following a strict governmental response (including isolation of infected persons for at least ten days, regimented sanitary practices in place in healthcare settings, strict de-contamination of all shipments, and travel alerts for impacted areas) (Centers for Disease Control and Prevention (CDC) 2013) the transmission was halted and no confirmed cases have been reported since January 2004 (Gralinski and Baric 2015). In December 2019, SARS-CoV-2 is thought to have surfaced in the Huanan seafood market located in Wuhan, China (Worobey *et al.* 2022) . On December 31 of that year, the Wuhan Municipal Health Commission identified the outbreak as a novel coronavirus (Mackenzie and Smith 2020). As of June 2022, there were over 528 million confirmed cases and roughly 6.29 million deaths globally (Medicine 2020). Since SARS-CoV-2 is a virus that impacts the respiratory system and has an incubation period of two to fourteen days, governments worldwide have implemented laws requiring face masks to be worn in public to prevent the spread of the virus, as well as other social distancing measures (National Center for Immunization and Respiratory Diseases (NCIRD) 2020). While previous coronaviruses impacted infants, elderly people, and immunocompromised people at higher rates (Gralinski and Baric 2015), those suffering from chronic kidney disease, diabetes, cardiovascular disease, and chronic respiratory disease also appear to be at higher risk for SARS-CoV-2 infection (Clark*et al.* 2020).

In the first few months of the pandemic, it became clear that an accurate prediction of SARS-CoV-2 spread was important in establishing effective public health policies. Subsequently, numerous research and public health groups generated epidemiological models to predict the spread of the virus using various parameters and modeling methods (Ibarrondo *et al.* 2020). These models sought to forecast the daily and total cases and deaths due to COVID-19. Parameters included social distancing, shelter-in-place, business and school closures, and hygiene practices, among others. These models were expected to predict the spread of the virus in communities under different scenarios to guide public health policies.

Factors affecting the origination and spread of the outbreak . It has been particularly challenging to develop models that would capture the effect of increasingly virulent SARS-CoV-2 mutants observed in human populations (Chen *et al.* 2020; Wang, Wang and Zhuang 2020). For example, the B.1.617.2 variant, better known as the Delta variant, is 50% more contagious than the Alpha variant and is 75% more contagious than the original SARS-CoV-2. Thus, Delta also became a prevalent variant for many new COVID-19 cases in 2021 (Katella 2021). The Virus Outbreak Simulator for The US (https://bioinformaticshome.com/online_-software/virus-outbreak/US/index.html#) simulates the spread of select viruses; simulations were available for influenza, coronaviruses, and Ebola (Andrews 2019). We employed this server to run simulations using the settings summarized in **Table 3** . The simulation was set so that the total population was 327 million people and on Day 1, there were 55k carriers of each virus. The coronavirus numbers used by the simulation have been updated daily since December 2019 and were taken from the Institute for Health Metrics and Evaluation (https://covid19.healthdata.org/projections) projections (Institute for Health Metrics and Evaluation 2021).

Table 3. The standard settings for the Virus Outbreak Simulator.

Parameter	Ebola	Coronavirus	Influenza

Parameter	Ebola	Coronavirus	Influenza
Duration (days)	16	126	96
Virulence	2	50	50
Lethality	50	5	0.5
Incubation time	10	5	2
Infection time	5	9	4
Vaccination (%)	0	60	47
Containment	Quarantine and physical distancing	No containment	No containment

The numeric results of the simulations can be seen in **Figure 1** . While vaccinations played a significant role in the number of people predicted to be affected by influenza, only a tiny portion of the population was predicted to die from the infections. Similarly, only a small percentage of the U.S. population was predicted to be infected with Ebola, likely due to the full containment that was in effect for the Ebola simulation. While this severely limited the spread of the infections, all of these infected persons were predicted to die.

[CHART]

Figure 1 . Number of affected people in the United States based on the simulations of influenza, coronaviruses, and Ebola outbreaks (using https://bioinformaticshome.com/online_software/virus-outbreak/US/index.html#; see text for the input parameters used). All numbers are in millions of people, and the respective colors represent those who would be uninfected, vaccinated (when applicable), immune, and those who would die from the infection.

To understand the threat posed by the Delta variant, we aimed to simulate how it would impact the United States using the simulator under different conditions. Primarily, we varied the lethality of the virus and containment strategies and assumed that 47% of the U.S. population was vaccinated as of July 4, 2021 (Carlsen *et al.* 2021). We varied the containment, to view the effects of the reopening of the U.S. and vaccine distribution, and the lethality, to view the differences given the unestablished relationship between the lethality and the roughly 60% increased virulence of the Delta variant (Lovelace Jr. 2021). The input parameters and the results of these simulations are summarized in **Table 4** and **Figure 2** .

Table 4. Properties of the simulated Delta variant to hypothesize its effects on a large population, especially comparing lethality and containment efforts.

Parameter	Containment, Higher Lethality	Containment, Normal Lethality	No Containment, Normal Le
Duration (days)	65	60	124
Virulence	80	80	80
Lethality	8	5	5
Incubation time	5	5	5
Infection time	9	9	9
Vaccinat-ion (%)	60	60	60
Contain-ment	Quarantine and physical distancing	Quarantine and physical distancing	No containment

[CHART]

Figure 2. Number of affected people in the United States based on the simulation of the outbreak of a modified coronavirus emulating the Delta variant of SARS-CoV-2. All numbers are in millions of people, and the respective colors represent those who would be uninfected, vaccinated (when applicable), immune,

and those who would die from the infection.

These predictions demonstrate how important containment practices like quarantining and social distancing are. Even with increased lethality, containment decreases the number of fatalities by more than 200-fold. Furthermore, increased simulated vaccination significantly decreased the number of deaths (data not shown). Similar studies were run for the Omicron variant. Including the U.S. vaccination status (64%) as of Feb 16, 2022, we ran the same simulations, only adjusting the settings from our alpha SARS-CoV-2 model by increasing the virulence to 90% and decreasing the lethality to 3%. These percentages were chosen based on the several fold increase in contagiousness (Park 2022) and less than 1% average fatality rate seen in Omicron cases (Arnott 2022). Compared to alpha settings with 64% vaccination, Omicron reduced the duration of the simulated outbreak by 19% and the deaths by 87%. However, with full containment methods, both simulated outbreaks ended in 30 days (83% less than the previous alpha simulation) and left the vast majority of the population alive and immune.

Obviously, containment and vaccination are crucial factors in the impacts of SARS-CoV-2 on humanity. Furthermore, the individual specifications of each variant can provide a moving target for therapeutics and models alike. For example, a 3% change in lethality can lead to a 45% increase in deaths when there are no social containment measures. Therefore, rapid changes in containment, vaccination, and viral mutation present major complications to building successful models. Our simulation was limited by using flat vaccination rates as well as poorly defined containment procedures. The flat vaccination rate does not account for those who have been partially vaccinated or any growth in the number of people vaccinated over time. As for the containment, "quarantine" and "physical distancing" are not specific and leave room for interpretation. Notably, IHME COVID-19 data (Institute for Health Metrics and Evaluation 2021) were used to set up the parameters for isolation and social distancing in the simulation. We recognize these limitations and consider it essential to emphasize the importance of both interventions, especially in considering a more lethal virus.

Beyond the current variants of SARS-CoV-2, an impending SARS-CoV-3 should warrant further concern. One study (Wardeh, Baylis and Blagrove 2021) summarized the data of past transmission cases to highlight the probability of both a novel SARS-CoV outbreak event, as well as novel vector and species transmission. Then, the authors compiled and sequenced viral genomic data to compare it with potential mammalian vectors and generated models predicting each potential coronavirus-mammal association. In doing so, they suggest that dogs, rats, Chinese ferret-badgers, and the Asian palm civet, among more than 100 mammals, should be monitored as major potential host reservoirs for both MERS-CoV and SARS-CoV-2 mutation and transmission (Wardeh, Baylis and Blagrove 2021). Other studies (Wang, Wang and Zhuang 2020; Murray and Piot 2021) have also implied the threat of both continued SARS-CoV-2 and further mutations, but not all have built models to predict the future SARS-CoV outbreaks.

MERS-CoV (2012-2014)

History . In November 2012, van Boheemen *et al* . investigated a case of lung failure and death that resembled HKU4 and HKU5 coronavirus infections and discovered HCoV-EMC/2012, soon to be known as MERS-CoV (van Boheemen *et al.* 2012). The first confirmed case in the U.S. was on May 1, 2014, and the Middle Eastern outbreak began in mid-March 2014. On May 16, 2014, at the start of the U.S. outbreak, Bialek et al. (Bialek *et al.* 2014) published a warning (see **Table 1**) citing two MERS cases in the United States, one in Florida and one in Indiana, in the hopes of preventing a full epidemic in the U.S. (Bialek *et al.* 2014) (**Figure 2**). However, by mid-2014, the virus had spread and become an epidemic, with 1507 confirmed infections worldwide between 2014-2015, with a fatality rate of 35%. As of March 2022, there have been a total of 2589 confirmed cases (World Health Organisation 2020). These cases came from at least 26 countries, but the majority were in the Middle East and Korea (World Health Organization 2015). The original zoonotic transmission was facilitated by increased bat-to-camel and camel-to-human interactions consistent with increases in camel trading (Gralinski and Baric 2015). Precautions put in place surrounding human-camel interactions were estimated to have prevented over 1000 cases (Donnelly *et al.* 2019). While MERS-CoV was established as a threat in 2013, a search on PubMed (https://pubmed.ncbi.nlm.nih.gov/)

revealed that a camel-transmitted coronavirus was not discussed in the scientific literature until 2014 (Josset *et al.* 2013; Khan*et al.* 2013).

Factors affecting the origination and spread of the outbreak . Most of the focus on modeling the spread of MERS-CoV revolved around proper data mining and the allocation of patient information. The models were based on two key components, the patients' ages and whether they were symptomatic. These conclusions pointed towards older patients being at the highest risk of complications from MERS-CoV. The models based on these characteristics produced accuracies ranging from 53.6% to 71.58% (Al-Turaiki, Alshahrani and Almutairi 2016). However, publications describing modeling or forecasting MERS-CoV were extremely limited. We have identified a study describing an epidemiological model that concluded that hospital transmission cases were four times more influential to viral spread than community transmission. Written during the 2014 outbreak, the study suggested efforts to contain the then-current MERS-CoV should be focused on hospitals. They also shared an idea that the weak secondary MERS-CoV transmission removed its "epidemic" status based on the R$<$ 1 where secondary community transmission cases were concerned (Chowell*et al.* 2014)..

Dengue virus (DENV)

History . Dengue virus (DENV) originated in monkeys and spilled over into humans via *Aedes aegypti* mosquitoes around 100-1500 years ago (Teoh *et al.* 2010). This flavivirus was first isolated in 1943 during the dengue pandemic in Nagasaki, Japan by two scientists studying blood samples (Takasaki 2011), but it is suspected that a 1635 epidemic in Martinique and Guadeloupe may be the first known outbreak of the virus (Dick *et al.* 2012). DENV has four serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. People can contract dengue virus multiple times over the course of their lifetime and in some places where serotypes co-circulate, contracting different serotypes is not uncommon (Gubler 1998). A phenomenon called antibody-dependent enhancement (ADE) can occur when a secondary infection results from a different DENV serotype than the one that caused the primary infection. Antibodies are cross-reactive across DENV serotypes and can facilitate uptake via Fc-gamma receptors into privileged tissues. This phenomenon comprises ADE and can result in some of the severe pathologies associated with infection, such as dengue hemorrhagic fever. No antivirals currently exist to treat acute DENV infection. DENV vaccines exist but have limited efficacy due to the complexity of generating immunity against all four serotypes (Thomas and Yoon 2019).

From 1953 to 1954, the Philippines experienced a dengue fever outbreak that is believed to have catalyzed the spread of DENV throughout Southeast Asia. Tropical climates are conducive to mosquito living and breeding habits and therefore are usually the most susceptible to large vector-borne outbreaks. Central and South America, Southeast Asia, Central Africa, and the Caribbean have had numerous viral outbreaks. The annual infection rate for DENV is roughly 400 million people, including approximately 22,000 fatal cases (Centers for Disease Control and Prevention (CDC) 2019d). There are over 100 countries and 3 billion people worldwide that are at risk of contracting DENV (Centers for Disease Control and Prevention (CDC) 2020a). Combatting dengue fever relies on stopping outbreaks from getting out of hand through "active surveillance." Since DENV is transmitted via mosquitos, epidemics can be prevented by enforcing emergency mosquito control. In Brazil, a genetically modified *Aedes aegypti* mosquito containing a dominant lethal gene was developed and introduced to nature to control yellow fever, dengue, chikungunya, and Zika viruses. Follow-up genetic sampling after 30 months has shown evidence that portions of the genetically modified strain genome have been incorporated into the target population (Evans *et al.* 2019).

Factors affecting the origination and spread of the outbreak . Health authorities have also taken more precautions, like creating clinical networks to monitor DENV based on symptomatology (Gubler 1998). In Australia, predictive models have been used to show correlations between the Southern Oscillation Index (SOI), a measure of sea level air pressure difference between the eastern and western tropical Pacific, and dengue cases. A multivariate Seasonal AutoRegressive Integrated Moving Average (SARIMA) model was generated using Queensland Health and Australia's Bureau of Statistics data from January 1993 and December 2005. It was discovered that dengue fever cases increased as the SOI decreased and temperatures increased; their predictive model values matched observed cases with an error of 1.93% (Hu *et al.* 2010).

Models like these could be pivotal in other at-risk countries if data can be reliably collected.

Zika virus (ZIKV)

History . Zika virus (ZIKV) was first isolated in 1947 in Uganda and the first human infections were reported in Nigeria in 1954 (Dick, Kitchen and Haddow 1952; World Health Organization 2018). ZIKV infections typically occurred as sporadic cases and in small clusters until the 2007 outbreak in Yap (Micronesia) saw close to $\frac{3}{4}$ of the population infected (Plourde and Bloch 2016). As a mosquito-borne flavivirus, cases were mostly limited to Africa and Asia until 2015, when the virus was reported in Brazil and 29 other South American, Central American, and Caribbean countries. ZIKV is closely related to other flaviviruses such as dengue virus, Spondweni virus, and Kedougou virus. ZIKV is an arbovirus, a vector-borne virus carried by arthropods before transmission to vertebrate hosts. There are more constrains on arbovirus evolution because they must survive and replicate in two different animals, the human host and the arthropod vector. However, some evidence suggests that ZIKV can undergo recombination, potentially increasing its virulence and rate of evolution (Han *et al.* 2016; Dermendjieva *et al.* 2020). ZIKV is primarily transmitted by *Aedes aegypti* mosquitoes but it can also be sexually transmitted, vertically transmitted, and transmitted via blood transfusion (as in Brazil and French Polynesia), animal bites, or lab exposures (Plourde and Bloch 2016). In addition, climate change is allowing the *Aedes aegypti* mosquito, which transmits viruses such as dengue, Zika, and yellow fever, to spread to new areas, including the United States, putting them at risk for ZIKV endemicity (National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) 2018). While the current European climate does not support *Aedes aegypti* , climate change could eventually alter vector geographic distribution and allow this vector to partake in large-scale arboviral disease outbreaks (Liu-Helmersson *et al.* 2019). International trade and travel have increased the spread of the virus, as evidenced by the 2015-2016 epidemic. The 2015-2016 outbreak in Brazil was further exacerbated by the lack of effective treatments and vaccines (Plourde and Bloch 2016), which still to date, do not exist. ZIKV proved particularly dangerous due to the similarity in symptomology to other, co-circulating flaviviruses (DENV) and the initial uncertainty surrounding its connection to microcephaly in babies born to infected mothers (Heymann *et al.* 2016).

Factors affecting the origination and spread of the outbreak . Two major factors have been identified to explain the increasing global spread of the virus: urban transmission and stochastic factors. Experimental studies did not support a genetic variation hypothesis suggesting that an adaptive evolution of ZIKV was responsible for the rapid spread (Gubler, Vasilakis and Musso 2017). Rather, it is theorized that high levels of viremia in humans facilitates vector-borne transmission (Gubler, Vasilakis and Musso 2017). Newly infected, immunologically naïve populations were the most likely causes of rapid spread (Gubler, Vasilakis and Musso 2017), as it is assumed that infected individuals have lifelong immunity. Given the 2015-2016 epidemic timeline, the next outbreak is predicted to occur around 2035 (see **Table 1**), when reintroducing the virus to naïve populations in the Americas could lead to an outbreak; the chance for outbreaks goes above 50% in 2047 (Counotte *et al.* 2019). It is thought young women of reproductive age will be at the most risk for ZIKV in the future (Counotte *et al.* 2019) due to the particularly dangerous threat Zika poses to pregnant women and their unborn children. However, we could not identify any reliable simulations or models that could confidently predict future ZIKV spread.

Mayaro virus (MAYV)

History . Mayaro virus (MAYV) was first isolated from the blood of five patients in Trinidad in 1954 and also presents similarly to DENV (Anderson *et al.* 1957; de O Mota, Avilla and Nogueira 2019). These five cases of moderate febrile illness were isolated in August and September 1954; four of these cases were in forest workers in the southern Trinidad, and one was in a young girl living in the north (Anderson *et al.* 1957). The virus has since reappeared as outbreaks in Bolivia, Brazil, Ecuador, French Guiana, Venezuela, and Peru. In addition, it has even recently made its way to North America and Europe, largely through travel (Acosta-Ampudia *et al.* 2018). Given the nonspecific, typically mild symptoms of MAYV, it is difficult

to distinguish it from other arboviruses, and there is good reason to believe that many MAYV cases are diagnosed as other arbovirus infections. While Mayaro virus cases in humans have been found mostly in the Amazonian region and Central and South America, it has the potential to rapidly spread to many more countries and geographical areas (Acosta-Ampudia *et al.* 2018). MAYV has an extensive host elasticity and has been detected in several vertebrate reservoirs such as primates, rodents, and birds, which increases the likelihood of the virus spreading to other locations. While vectors and hosts have only led to rural outbreaks in tropical areas in the past, the transmission of MAYV in the future could become more urbanized (Acosta-Ampudia*et al.* 2018). A case of MAYV infection in Haiti in 2015 was found to be caused by a different MAYV strain, similar to ones isolated in Brazil, which was circulating in Peru, Bolivia, and other South American countries. This case demonstrated active circulation of MAYV in Central America and the Caribbean and raised concerns about the potential of MAYV spreading to the southern United States (de O Mota, Avilla and Nogueira 2019).

Factors affecting the origination and spread of the outbreak . Lack of an effective vaccine and documented spread to new regions increase the global risk of Mayaro virus outbreaks. Currently, vector control (the use of techniques to mitigate the transmitting species, in this case mosquitos) and personal protective measures are the only forms of infection prevention. However, these measures have not been very effective as the number of new arboviral infections continues to increase (Esposito and Fonseca 2017). Mayaro virus is more than capable of causing an outbreak in Brazil or the surrounding geographical areas (Esposito and Fonseca 2017). Efforts are being made to identify novel anti-MAYV drugs. One study identified 12 natural compounds with potent antiviral activity *in vitro* (Mahomoodally and Gurib-Fakim 2013). One group performed a biomathematical analysis on the epidemiological consequences of MAYV in Colombia (Valencia-Marín, Gandica and Aguirre-Obando 2020). Their model was based on the temperature, migration patterns, rates of development, and the flow of land cargo, all of which contribute to the vector spread and ability to infect the human population. Specifically, this study determined that regions with high rates of land cargo movement and temperatures between 23-28 °C were most at risk for Mayaro virus spread via *Ae .Aegypti.* Therefore, they concluded Magdalena, Imerí, and the biogeographical Chocó areas to be at the highest risk for rapid spread of MAYV in Columbia (Valencia-Marín, Gandica and Aguirre-Obando 2020).

Lassa virus (LASV)

History . First described in Nigeria in 1969, Lassa virus (LASV) is endemic to seven West African countries and causes Lassa hemorrhagic fever; out of approximately 300,000 annual cases, there are an estimated 5,000 deaths (Ilori *et al.* 2019). The Lassa fever outbreak in 2018 occurred in Nigeria and most fatalities were in elderly patients. Of the over 450 laboratory-confirmed cases (1800 total cases), the fatality rate without the prescription of Ribavirin was over 70%; with this treatment, the fatality rate dropped to roughly 25% (Ilori*et al.* 2019). Sequencing of the blood samples taken during this outbreak suggests rodent reservoir spillover instead of human-human transmission (Du Toit 2018). A lack of research and diagnostic capacity in Lassa fever detection may have led to underreporting of cases in this outbreak (Ilori *et al.* 2019). An enzyme-linked immunosorbent assay is the main form of diagnosis for Lassa fever. The time lag present between symptom onset and diagnosis was found to be approximately one week (Ilori *et al.* 2019). The Nigeria Center for Disease Control partnered with the WHO to limit the transmission in this outbreak through clinical case management, contact tracing, and local public health support. However, prevention without vaccines is proving difficult. The Coalition for Epidemic Preparedness Innovations (CEPI), funded by the Wellcome Trust, national governments, and the Bill & Melinda Gates Foundation, have focused on developing a Lassa vaccine (Du Toit 2018), but have not yet delivered past phase I clinical trials (The Coalition for Epidemic Preparedness Innovations 2021).

Factors affecting the origination and spread of the outbreak . The major risk areas of Lassa virus outbreak are Sierra Leone, Liberia, Guinea, Nigeria, and other countries in the region (Fichet-Calvet and Rogers 2009). This was determined by environmental data and statistical analysis, as these have proven to be the most effective method of producing Lassa fever risk maps (see **Table 1**). Models were generated using

non-linear maximum likelihood discriminant analysis techniques. Areas of presence and absence of Lassa fever were identified in West Africa, which considers the distribution of the highly populous rodent hosts (Fichet-Calvet and Rogers 2009). These models were designed to distinguish the presence of the virus in humans, however, not in the hosts. The survival of LASV in decreased humidity significantly increases its transmission potential. Rainfall conditions appear to have the most substantial influence, but the temperature has a variable impact, especially in high-risk areas of Western Africa (Fichet-Calvet and Rogers 2009). A new hemorrhagic fever similar to Lassa fever was observed in Soviet workers in the 1940s and then reappeared in Asia and South America throughout the 1950s (Monath 2019). Each case was similar in that they coincided with human-caused, ecological disturbances, and rodents were the reservoir host in the majority of the outbreaks (Monath 2019).

Noroviruses

History . Noroviruses are responsible for 58% of foodborne diseases in the United States, causing 21 million cases and 900 deaths annually (Centers for Disease Control and Prevention (CDC) 2020b). Globally, there are 125 million cases of norovirus foodborne illness every year. There are many techniques for predicting outbreaks, including both *in vivo* and *in vitro* testing; however, there is not a single golden technique or standard (Manuel, Moore and Jaykus 2018). Because norovirus is highly contagious, it is of concern in any country where food contamination is prevalent. Hence, it is seen in both commercially processed food in developed countries and locally sourced food in poorer countries (Saljoughian 2016). Despite its significance, no antivirals or vaccines currently exist to treat norovirus.

Factors affecting the origination and spread of the outbreak . Some norovirus outbreaks can be predicted using factors specific to the host of the norovirus. For example, oyster-borne norovirus can be monitored and predicted using an Artificial Neural Network model called NORF (Wang and Deng 2016). The authors successfully used the NORF model to predict these outbreaks to take place on the Gulf of Mexico using environmental factors such as salinity, water level height, temperature, wind, and rainfall (see **Table 1**). The model was trained on 14 years of data (from 1994-2007) and validated using seven additional years of data (from 2007-2014). Using the training set data only, the model predicted that an outbreak on the Louisiana coast would occur on December 29, 2013. Indeed, the outbreak occurred from December 26, 2013 to January 9, 2014 (Wang and Deng 2016). While this was retrospective in nature, the model was successful in predicting a confirmed outbreak from external data. Given their success in predicting previous outbreaks, these and other risk assessment models considering water irrigation of produce (Fiona Barker *et al.*2013) could potentially be used to predict future outbreaks. Collaborative tools such as NoroNet, a scientific surveillance collective for norovirus (*https://www.rivm.nl/en/noronet),*may also help identify outbreaks before they occur. Another model called NOROCAST was created in Japan to predict norovirus genotype and herd immunity; this model found that the structural protein 1 impacted herd immunity the most and should be targeted for therapeutics (Suzuki*et al.* 2019).

Influenza virus

History . Influenza virus has existed for centuries, and has remained in the human population through its rapid mutation rate and resultant ability to evade the human immune system (Francis, King and Kelvin 2019). The processes by which the influenza virus evolves are known as *antigenic drift* and *antigenic shift* . Antigenic drift is the gradual process by which an influenza strain mutates to avoid the human immune system year by year, necessitating the development of annual vaccines. Antigenic shift is more drastic and is usually the result of two different influenza strains recombining their genetic material to form an entirely new virus type (Centers for Disease Control and Prevention (CDC) 2019e). Influenza viruses are named according to their combination of hemagglutinin (H) and neuraminidase (N) protein subtypes encoded in their genomes. The human population is practically naïve to this new virus so it can cause devastating outbreaks such as the H1N1 1918 flu pandemic. This was the first devastating influenza outbreak, claiming

roughly 100 million lives. Many factors contributed to this outbreak, such as the mass migration and crowded conditions among soldiers in World War I (Centers for Disease Control and Prevention (CDC) 2018).

Other notable influenza outbreaks in history include the H2N2 pandemic in 1957, which killed over 1 million people, and the H3N2 pandemic in 1968, which saw a death toll of 1 million people. The U.S. observed lower fatality rates in the 1968 H3N2 pandemic, attributed to existing N2 antibodies used to combat the 1957 H2N2 outbreak (Neumann and Kawaoka 2019). However, these strains continued to circulate worldwide and led to the development of a novel H1N1 influenza strain (Christman *et al.* 2011), which caused the 2009 pandemic dubbed the "swine flu" because it was transmitted from pigs to humans (Coburn, Wagner and Blower 2009). The 2009 H1N1 pandemic was considered one of the worst pandemics in the 21st century, claiming somewhere between 150,000-500,000 lives worldwide (Centers for Disease Control and Prevention (CDC) 2019c).

Factors affecting the origination and spread of the outbreak . The natural reservoirs of the influenza virus are wild birds and waterfowl, but domestic poultry and swine can also serve as reservoirs for this virus. Avian influenza does not typically spread to humans, but generally is more virulent than other viral strains when it does manage to make this zoonotic jump (e.g., H5N1, H7N9) (Roguski and Fry 2017). There are now four antiviral drugs specifically approved for use against influenza: oseltamivir, zanamivir, peramivir, and baloxavir (Roguski and Fry 2017). Annual vaccination against seasonal influenza is available in many countries to protect against the predicted strains in that year. Unfortunately, it is difficult to predict what strains will emerge, so these vaccines typically have lower efficacy than other vaccines against more static viruses (National Center for Immunization and Respiratory Diseases (NCIRD) 2022). It is believed that the most proactive response to preventing the next influenza resurgence is to survey wild birds actively and observe how they interact with domestic animals and humans (Taubenberger and Morens 2010). Many models integrating past mutation data and other creative tactics, such as local search query data, have been built to predict the next pandemic flu strain (Łuksza and Lässig 2014; Zhang *et al.* 2019; Yin *et al.* 2020), all claiming limited success, but acknowledging the stochastic nature of the influenza virus evolution and the plethora of data needed to build models. For instance, Yin et al. (Yin *et al.*2020) employed their model to predict mutations of influenza A viruses. They found they can predict point mutations at selected residues and found their model provided better insights than current methods.

Nipah virus

History . Nipah virus is a paramyxovirus endemic to Southeast Asia that features exceptionally high human-to-human transmission rates in some areas (Clayton 2017). Fatalities associated with the virus are frequently due to encephalitis (Ang, Lim and Wang 2018). There are no effective antivirals to treat Nipah virus (Sharma*et al.* 2019) and mortality rates range from 32-92% (Singh*et al.* 2019). The first outbreak was in Malaysia in 1998-99 and has not returned to Malaysia since, whereas places like Bangladesh and India see yearly emergences (Clayton 2017; Ang, Lim and Wang 2018). Nipah virus is transmitted from person to person primarily through bodily fluids, transmission easier to control if the patient is aware of their illness. Therefore, effective containment is typically dependent on patient isolation (Nikolay *et al.* 2019).

Factors affecting the origination and spread of the outbreak . In nature, the primary reservoirs of the Nipah virus are flying foxes, a large bat of the genus *Pteropus* (Lo Presti*et al.* 2016). Recent outbreaks in Bangladesh and India trace back to contaminated date palm sap (Ang, Lim and Wang 2018). An intermediate host that facilitates the transmission of the virus from bats to humans is pigs; the 1999 outbreak in Malaysia resulted in a massive, nationwide culling of pigs to halt the spread of the virus. As they are a frequent host of human-threatening virulent diseases, many studies monitor swine for pathogens hoping to stop the next viral outbreak before it occurs (Ruiz-Fons 2017). Geographical mapping considers climate, longitude, latitude, and previous outbreaks to predict the next outbreak (Peterson 2015).

Hantaviruses

History . The first hantavirus outbreak took place during the Korean War and lasted approximately three years. Around 3,000 American soldiers fell ill and approximately 7% died, with a common symptom being renal failure. In 1973, a New World hantavirus caused an outbreak in the United States' Four Corners region (Arizona, Colorado, Utah, New Mexico border). The striped field mouse was identified as the primary reservoir (Muranyi *et al.* 2005), and it was determined that humans contract the Four Corners virus when feces and/or urine from infected animals is aerosolized (National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) 2020a). Through this discovery, hantaviruses were linked to unidentified cases in various other countries like China, Russia, and South Korea (Old World hantaviruses). It is estimated that there are 150,000 cases of hantavirus infection each year, mainly in Asia. The primary disease state induced by New World (Americas) hantavirus infection is Hantavirus Pulmonary Syndrome (HPS), which is characterized by severe noncardiogenic pulmonary edema (Peters, MD, Simpson, MD, PhD, MPH and Levy, MD, PhD 1999). The disease state commonly induced by Old World hantaviruses is hemorrhagic fever with renal syndrome (HFRS), in which patients typically display a vascular leak of the retroperitoneum and kidney tubular necrosis, leading to conjunctival injection. In both cases, patients also typically show signs of myocardial depression, hypotension, and/or shock; in both HPS and HFRS, symptoms typically consist of fever, myalgia, malaise, and gastrointestinal issues (Peters, MD, Simpson, MD, PhD, MPH and Levy, MD, PhD 1999). The overall mortality rate of HPS is 38% (National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) 2016). More than 21 hantaviruses are known to infect humans, with symptoms ranging from hemorrhaging to pulmonary edema (Muranyi*et al.* 2005).

Factors affecting the origination and spread of the outbreak . Most approaches to predict hantavirus outbreaks depend on examining the relationships between rodent population growth and hantavirus exposure. These models consider aspects such as random mating and deaths relating to disease or natural causes. Mathematical models have been developed to analyze and interpret the interaction between rodents and hantavirus (Jonsson, Figueiredo and Vapalahti 2010). These models are epidemiologically base (SIR and SEIR models), and the hope they will predict hantavirus outbreaks with higher accuracy than animal models of transmission (Jonsson, Figueiredo and Vapalahti 2010). As is common for many viruses, animal models tend to be unreliable due to their inability to accurately represent humans, or fail due to ethical, safety, or financial reasons. Furthermore, they are even more difficult to standardize or apply to populations (Safronetz, Geisbert and Feldmann 2013). Therefore, in silico models based on human data are preferred. Other sources posit that adding seasonal interactions with rodents is crucial to models when trying to predict outbreaks (Sauvage, Langlais and Pontier 2007). It is also notable that there is increased interaction with rodents as the human population grows and more rodents flock to urban areas due to the destruction of their ecosystems (Neiderud 2015).

Oropouche virus (OROV)

History . The Oropouche virus (OROV) was first isolated in 1955 in Trinidad and Tobago. The rate of infection is likely underreported due to its symptomology (fever, headaches, and muscle/joint pain that develop into meningitis) being similar to that of many other arboviruses (Gutierrez *et al.* 2019). The spread of the OROV has gained attention from researchers as it has become associated with climate change, globalization, human travel, and animal transport. The virus has reemerged multiple times in Central and South America and has caused more than 30 epidemics in the area; more than half of a million people have been infected by OROV in the last sixty years but since viruses like dengue, chikungunya, and yellow fever co-circulate in the same endemic regions, many cases likely go undiagnosed (Silva-Caso*et al.* 2019). It is predicted that outbreaks and sporadic cases will increase in Brazil and the Amazonian region over time, largely due to recent wildfires and rapid deforestation (de Oliveira Andrade 2019; Tollefson 2020). Because these tropical regions are amenable to the arthropod vectors, such as mosquitoes, that spread this virus, zoonotic arboviruses can cause great harm in these areas. The densely populated region of southeastern Brazil also has a higher risk of an outbreak due to internal and international migration and tourism (Vasconcelos*et al.* 2001; Lowe *et al.*

2013)

Factors affecting the origination and spread of the outbreak . OROV causes a self-limited, acute, febrile illness known as Oropouche fever that lasts 2-7 days and can result in 2-4 weeks of physical weakness. Immunocompromised individuals are at a higher risk for severe cases, but the disease affects people of all ages (Sakkas*et al.* 2018). In addition, the currently available treatment is only palliative, which can ease or reduce symptoms but cannot directly impact the replication of the virus within the body. Because no human vaccine exists, the only prevention strategies are vector control and eradication measures. Given that personal protection cannot entirely prevent the spread of infection by mosquitos, the virus can be hard to control and contain. Evolving environmental, demographic, and social factors make it likely that OROV will spread outside Central and Latin America in the near future (Sakkas *et al.* 2018). Despite our growing knowledge of the epidemiological, clinical, and molecular features of OROV, at this point we do not have sufficient foundations to develop treatments. This is largely due to the non-fatal pathogenesis of OROV infection and its primary involvement with the CNS (da Rosa*et al.* 2017).

Marburg virus (MARV)

History . The first filovirus ever described was the Marburg virus (MARV); this virus was isolated from a series of cases in Germany and Serbia in 1967. Patients described their symptoms as extreme malaise, headache, and fever. After a week of illness, additional symptoms began including nausea, vomiting, and diarrhea. All fatal cases had signs of hemorrhaging (Slenczka and Klenk 2007). The 1967 outbreak in Germany and Serbia was associated with research-related exposure to African green monkeys imported from Uganda. Other outbreaks and sporadic cases with incredibly high fatality rates (227 deaths out of 252 cases) occurred in Angola, the DRC, Kenya, and Uganda between 1980 and 2005, (Slenczka and Klenk 2007). MARV outbreaks are thought to originate mostly from exposure to Rousettus bat (African fruit bat) colonies. The virus can be contracted through direct contact with infected individuals, bodily fluids, and contaminated surfaces/materials(World Health Organization 2017).

Factors affecting the origination and spread of the outbreak . While the broader epidemiology of MARV is unknown, at this point, non-human primates have not proven susceptible to the disease, unlike the Ebola virus (Valentine *et al.* 2020). The majority of human outbreaks occurred due to spillover events in caves and mines. But, as is common with other viral hemorrhagic fevers, a failure to rapidly diagnose cases leads to the potential for transmission originating in a hospital or healthcare facility (Pigott *et al.*2015). No vaccines or antiviral medications are currently approved for MARV. Predictive models, that use transmission maps with calculated uncertainty, forecast East Africa as the main region of concern for future outbreaks (Peterson and Samy 2016). The models were built using Maxent ecological niche modeling, and uncertainty was determined by testing 25 random points, bootstrapping, and calculating the median and range. However, they are limited by time-averaging all the data used, as well as the access to ecological, viral, and vector data for some of these regions nearly 20 years ago.

Ebola (1976, 1979, 1994,-1997, 2000-2003, 2014-2016, 2021)

History . Ebola viruses were originally isolated in 1976, from two independent, overlapping outbreaks in south Sudan and the Democratic Republic of the Congo (formerly Zaire) (Feldmann *et al.* 2003). It continued to plague West African countries with estimates of less than 400 cases per breakout, until the 2014 Zaire Ebola virus led to mass panic and ravaging casualties in West Africa. This outbreak affected roughly 29,000 people in West Africa (specifically Sierra Leone, Guinea, Liberia, Nigeria, Mali, and Senegal) for 13 months between 2014 and 2016 and held a 33% mortality rate (Wing *et al.*2018; Bempong *et al.* 2019). The World Health Organization was criticized for its delayed reaction to this epidemic, especially given its magnitude. Many other factors contributed to the severity of this epidemic including limited resources, frequent travel over international borders, untrained health professionals, and mistrust of government officials and medical professionals (Wenham 2017).

In part due to Africa's tropical climate and ecosystems, many parasitic infections that produce similar symptoms, like typhoid and malaria, thrive in the areas where Ebola surfaced. For this reason, it is difficult to distinguish between these diseases when assessing a patient's symptoms. In addition, these patients tend to be grouped for treatment due to a lack of infrastructure and funding, making it difficult to determine the actual cause of death (Augier *et al.*2016). While there are home protective kits that can reduce the transmission in infected homes and areas (in some cases by up to 90%), they are not entirely effective and are not in mass distribution (Lewnard *et al.* 2014). A more recent Ebola outbreak occurred from February 14, 2021 to June 19, 2021 in Guinea causing only 16 confirmed cases, seven probable cases, and 12 deaths, due to a quick response by both the local government and the WHO, in conjunction with 24,000 vaccine doses (World Health Organization).

Factors affecting the origination and spread of the outbreak . Currently, reports say that 22 countries in Central and West Africa have the potential for zoonotic transmission (Gulland 2014; Pigott *et al.* 2014). Many forecasting tools, such as stochastic models and Susceptible-Infected-Recovered (SIR) approaches, were used in the wake of the 2014 outbreak and have continued to be tested and optimized (Asher 2018). Six months after the first reported case, the CDC stated that if nothing changed behaviorally, West Africa could expect 1.4 million cases (Meltzer *et al.* 2014). Before all of this, in 2004, Leroy et al. (Leroy 2004) discussed the trend in Ebola-infected apes and how these trends should be surveyed for predictions of human infection. They concur that the virus originated from wildlife, specifically great apes, near the Ebola River. The animals who contracted the virus were handled or hunted by local villages which led to the transmission of the virus (Leroy 2004). At least 14 established outbreaks prior to 2014 (LEGRAND *et al.*2007) seem to suggest that the virus is spread through local wildlife. In fact, one group claims to have alerted local health authorities to the severe risk of both the December 2002 and November 2003 human outbreaks well before they occurred (see **Table 1**). They identified these villages as having potential for an outbreak using their Animal Mortality Monitoring Network, an epidemiological surveillance network that was set up to identify infected hosts before they reach the human populations. The two predictions made (based on the data of the five previous outbreaks) were considered accurate, with both occurring in the predicted locations and within a few weeks or a few months later (Rouquet *et al.* 2005). In 2014, the same group published the approach on how to predict human outbreaks based on ape fecal samples from 2005 and 2007 (Reed *et al.* 2014). (Kuisma*et al.* 2019) implemented animal monitoring programs with the government and education programs with the locals in the Democratic Republic of the Congo as an attempt to prevent or lessen the next outbreak, but the system has yet to be tested as there has not been an outbreak in this location since the implementation.

When creating predictive models, the most crucial step is acquiring data properly. One Ebola model uses a mimicking system to test the viability of an outbreak in certain areas synthetically. This systems considers different transmission routes such as direct contact, vector-borne, and enteric transmission (Viboud *et al.* 2018). Variable symptoms should also be noted when improving the accuracy of these models, as more symptoms involved in the model could cause the accuracy to diminish. Constant surveillance and epidemiological characteristics are necessary to define the accuracy of these models (Hart *et al.*2019).

Accuracy of Outbreak Prediction Models

A few models were able to predict respective outbreaks within a month's precision (cf. Table 1). We note that while models offering long-term forecasts were not very successful, short-term models based on environmental changes and/or known wildlife patterns have been more accurate. The two most accurate models detailed in this review were the epidemiological surveying network and statistical models which displayed day level precision. The NORF model (Wang and Deng 2016) was able to use environmental factors to predict when the virus would flourish and transmit to humans through food, whereas the Ebola surveying network managed to alert local governments of human contamination with infected wildlife (Rouquet *et al.* 2005) with sufficient time prior to both outbreaks. While the success of the governments' interventions varied, the

models made reasonably accurate forecasts. Thus, the surveillance models, especially those monitoring the spread of viruses between humans and animals, have demonstrated their worth and should be researched and supported more widely (ScienceDaily 2021; Wille, Geoghegan and Holmes 2021). This was echoed again recently by researchers who found 35 cases of a henipavirus, named the "Langya" virus, from the last four years; they assert the importance of global viral surveillance models given the frequency of human-animal viral transmission (Mallapaty 2022).

Many factors might affect the predictivity of these types of models. Similar models should be considered for future predictive tasks. Due to differing viral evolution rates, distinct spillover events, and specific vector-host interactions, the most significant factors of highly predictive models are commonly virus-specific. However, some of them can be generalized, including epidemiological surveillance measures and monitoring climate change and other forms of human-induced disruptions to the natural order. These environmental factors are frequently indicative of viral spread as they relate to the abundance of the virus or its ability to transmit. Where possible, these should be considered heavily, especially in areas highlighted in **Figures 3** and**4** . For both these figures, we compiled information from the literature to identify countries that are within reasonable risk for certain outbreaks. We then generated maps highlighting countries identified in the literature. Neither of these maps should be considered as predictions. Rather, they are observation-based risk maps with no assumed date, exclusively based on literature and prior trends. In**Figure 3** , we use a map to visualize areas where outbreaks have occurred (both in origination and spread) to signify the impact of these viruses on the human population. We recognize that this information may be incomplete due to the prerequisite of proper testing and reporting that would allow one to find information on these viruses. Therefore, this knowledge is limited in that not all at past outbreaks may be included in any study and may be missing from the data. For updated alerts, websites like healthmap.org (https://www.healthmap.org/en/) provide a map with classified alerts based on literature and news reports. In **Figure 4** we recognize these same shortcomings, especially in considering areas at risk for being the origin of novel outbreaks but aim to emphasize how imminent viral threats are.

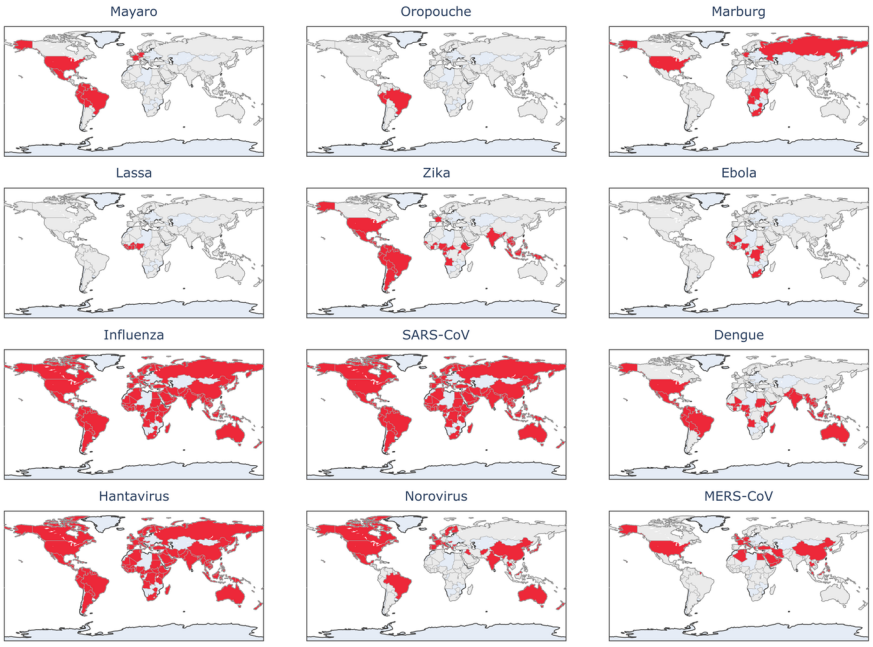

Figure 3. Map highlighting countries that either have experienced or been impacted by outbreaks of the selected viruses (National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) 2014a, 2014b; Verhoef *et al.* 2015; Acosta-Ampudia *et al.*2018; Sakkas *et al.* 2018; National Center for Immunization

and Respiratory Diseases (NCIRD) 2019; National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) 2020b).

As seen in Figure 4, the prevalence of outbreak risks, particularly in Brazil, China, and the United States, is clear and should raise concerns over rapid globalization, deforestation, and urbanization. Conversely, there are few parts of the world that are not dealing with the imminent threat of originating a viral outbreak. This further emphasizes the need for collaborative, worldwide research. As we learned with SARS-CoV-2, viral threats can grow quickly and become a concern for the entire world. A hot spot for these threats, Brazil has not only had the highest number of past outbreaks, but it also appears at risk for most future outbreaks. In combination with the tropical climate, deforestation exposes human populations to new species (and therefore new pathogens) by destroying the natural habitats in which reservoir hosts live. As seen with the SARS-CoV-2 pandemic, globalization is integral to spreading an emerging virus. Relatedly, environmental changes and technological advances (such as those contributing to globalization and property development) were also discussed in relation to Zika and Oropouche viruses (Vasconcelos *et al.* 2001; Lowe *et al.*2013; Liu-Helmersson *et al.* 2019). Factors like these should be heavily weighed when considering viral forecasting. There is much evidence connecting increased development and associated loss of biodiversity to an increasing number of disease outbreaks. Deforestation and extinction make pandemics and viral outbreaks more likely, as the species that survive and migrate during severe ecological changes are more likely to host pathogens (e.g., bats, rats, and birds) (Tollefson 2020; Carlson *et al.* 2022). Globally, it is estimated that sudden (on an ecological timescale) changes in climate and land use will drive new interactions between humans and zoonotic viral host species, resulting in 4000 cross-species transmission events for novel viruses by year 2070. (Carlson *et al.* 2022) For these and many more reasons, all viruses mentioned here are imminent threats, in addition to the emergence of new viruses and mutations.

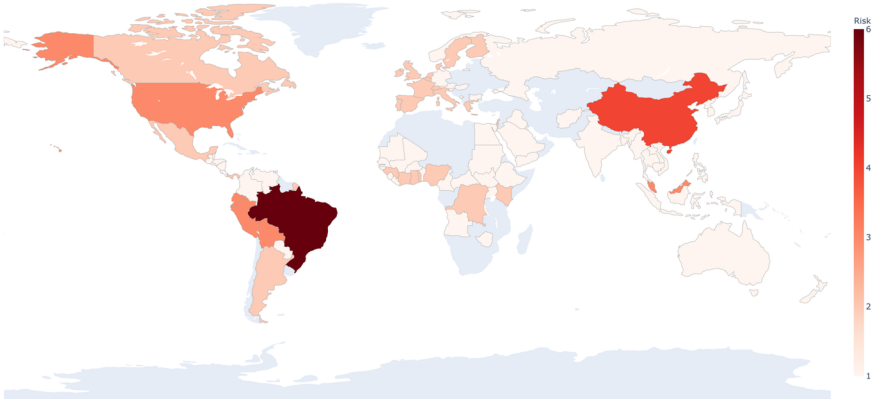

Figure 4. Visual representation of countries most at risk for originating new viral outbreaks, based on observed trends from previous outbreaks and literature describing those outbreaks. The darker the color and higher the number, the more at risk the country is at for being the epicenter of a novel outbreak. The lack of color in several countries does not imply safety, but rather there is no data or models implying to be at risk for the origination of a novel virus.(Gulland 2014; Lewnard *et al.* 2014; National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) 2014a, 2020b; Clayton 2017; Jiang*et al.* 2017; World Health Organization 2017; Sakkas *et al.*2018; de O Mota, Avilla and Nogueira 2019) This map does not reflect the viral spread that may cover neighbor countries or all the world, depending on the virus and medical counter-measures.

It is indisputable that there will be a plethora of viral outbreaks to come. However, learning from the past and using modern technologies, it may be possible to help mitigate the impact of these outbreaks. Whether this comes from predictive models, monitoring of wildlife, or pre-emptive drug discovery and development, we must continue to adapt and learn from what has been successful in the past. Moving forward, models

should aim to include as many salient factors as possible and rely heavily on data from previous outbreaks (Drake 2021), as well as animal and viral surveillance wherever possible. In 2020 and 2021, the world lost well over four million people to SARS-CoV-2 alone and, despite the vaccination and all other efforts, the outbreak is not yet defeated in 2022. It is crucial that we better understand how to prevent unique viral pathogens from emerging in the future. The predictive models discussed herein demonstrate that it is possible to predict pandemics with some accuracy before they occur, but it is also important that policy makers and other leaders listen to scientists performing this work and act upon it to prevent massive loss of life based on social measures (masks, distancing, etc.) as well as preventive development of drugs, especially broad-spectrum antivirals, and vaccines. In the past, hesitancy over drug resistant strains has halted development of antivirals (De Clercq 2005); our experience with COVID-19 exemplifies how important it is to continue and broaden this type of research. Although mutations and alternate strains of viruses cannot always be predicted (e.g., influenza virus), scientists' warnings should be heeded when they are well-founded. As the current practice showed, once the viral outbreaks occur, the best way to contain them is through diligent quarantine, disinfection, and travel restrictions.

While we continue to look to the future and the possibilities for viral outbreaks, we need to admit that there is no blanket approach to predict these outbreaks. Therefore, we must, in no way, relinquish neither hope nor readiness for discovery, but acknowledge that we will not precisely know what, when, and where the next viral threat will happen. COVID-19 taught humanity that new enemies are always waiting at the gate and will show no mercy. We have been warned, but now we need to be armed; antiviral drug discovery and development must be of the highest importance.

Summary and Perspectives

Viruses have always been present alongside humankind and new outbreaks are constantly happening. In addition, ecological disruption and climate change make it more likely that new zoonotic viruses will jump over to humans. However, as mentioned in this Perspective, there are many ways we can prevent these outbreaks from turning into mass tragedies, such as the 1918 flu pandemic and the current COVID-19 pandemic. Such methods include employing data science to predict emerging outbreaks, surveillance of reservoir populations, promoting scientific awareness and literacy, following guidelines set by scientists and officials as to how to prevent infection and spread, providing consistent funding for virology and broad spectrum antiviral drug discovery research, and ultimately heeding the warnings of the virologists and data scientists that forecast the occurrence of such outbreaks. For instance, where the NOROCAST predictions were heeded, potentially hazardous food was not distributed, and the impending illness was therefore prevented (Wang and Deng 2016); on the contrary, the warnings against MERS in the U.S. were not acted on promptly and severe illness struck those infected in the following months (Bialek *et al.* 2014; Donnelly *et al.*2019).

Due to the variable nature of the term "outbreak," it is crucial to understand the scope of the underlying event. The coexistence of humans and viruses is an intrinsic aspect of life. Epidemics of various sizes have occurred throughout recorded history and undoubtedly will continue to occur in the future. The constant increase in globalization, encroachment on wildlife, and climate change are all likely to increase the spread of emerging viruses (Baker *et al.* 2021). Therefore, it is essential to establish a long-standing political and financial investment in virology research to understand the etiology of new viruses and predict geographical areas and circumstances in which outbreaks are more likely to occur. Additionally, ongoing research is necessary to advance vaccine development as well as both broad-spectrum and targeted antiviral treatments. The time a country or community might have to combat a virus may be minimal, making this an extremely urgent task.

Outbreak analytics is an emerging research area focused on employing data science technology and methods to collect, curate, visualize, model, and report outbreaks to inform better and drive proper epidemiological response (Polonsky *et al.* 2019). However, as discussed in this perspective, current efforts have relied on forecasting new cases likely to arise, spread, and impact an ongoing outbreak. We posit that efforts should

be made to employ data science to predict the date and locale that emerging pathogens are more likely to appear to enable pointed research and public health efforts to prevent outbreaks from happening. The rapid and ubiquitous use of smartphones and heavy accumulation of social media data, electronic health records, surveillance and geospatial systems, health sensing systems, online search, and Bluetooth exposure apps (Google) have created an unprecedented technological infrastructure for achieving this goal, similarly to the prediction of other temporal catastrophic events, such as natural disasters (Goswami *et al.* 2018), terrorism (Ding*et al.* 2017), and urban pipeline leakage accidents (Qiu, Liang and Zhang 2018). Although the use of health data and phone location continues to raise privacy concerns (Schomakers, Lidynia and Ziefle 2019), progress has been made to develop privacy-preserving technologies to allow health data for contact tracing and epidemiological surveillance and outbreak analytics (Altuwaiyan, Hadian and Liang 2018; Anjum *et al.* 2018).

Before computational models can be considered a reliable data-driven approach for forecasting emerging pathogens, several steps in the data science of outbreak analytics should be executed. Ideally, data generated by different countries should be shared through government and research institutes, industry, etc., following the FAIR (findability, accessibility, interoperability, and reusability) data principles (Wilkinson *et al.* 2016). The logistics underlying building technologies able to predict future outbreaks are complex and will involve the development of both point-of-care data collection, database design, mobile apps, network infrastructure, privacy-preserving technologies, and the development of knowledge graphs algorithms. An epidemiological data model with a defined and well-established ontology needs to be developed to guarantee a good data ecosystem.

Biomedical knowledge mining tools like ROBOKOP (Bizon *et al.*2019) (**R** easoning **O** ver **B** iomedical**O** bjects linked in **K** nowledge-**O** riented**P** athways) and Chemotext (Capuzzi *et al.* 2018) have been developed to help elucidate biological pathways underlying compound activity or toxicity. Similar technologies can be leveraged and deployed to mine data to detect emerging pathogens and estimate data of new outbreaks to facilitate rapid responses, such as patient isolation and contact tracing to prevent the spread of the virus. For example, a recent study reported the development of a tool leveraging deep learning and a computer sensor system capable of predicting influenza outbreaks 15 weeks in advance based on and real-time data of flu patterns and symptoms (Al Hossain *et al.* 2020). The contact tracing apps for COVID-19 have faced low efficacy due to the low usage and testing rates (Cebrian 2021; Munzert *et al.* 2021). These recent studies have shown that data science can be used to better predict and assess the current state of outbreaks. Still, significant political and economic commitment to providing infrastructure for diagnostic testing, collecting, and evaluating the resulting data is necessary.

Another way to support disease prevention is through surveillance of viruses circulating within the human population and in reservoir/vector species in nature, when applicable. As seen with the influenza virus, surveillance of wild bird populations has been a proactive measure by which we can capture influenza virus diversity in nature. This information can be integrated into models that employ modern artificial intelligence technologies to predict what mutations may occur next or what unique strains might be assembled in these animal species that could infect and cause disease in humans.

Interest in viruses should not be a temporal issue, dependent on whether a viral pathogen is currently circulating through the population or not. However, it tends to be in many cases (Bobrowski *et al.* 2020). Scientific literacy and understanding how viruses and other pathogens cause human disease and spread throughout populations are necessary to promote widespread health. Vaccines are available for viruses that will cause outbreaks in the future, such as Ebola virus and influenza virus, and new vaccines for others are on the way. Widespread scientific literacy can facilitate the implementation of mass vaccination campaigns that will prevent outbreaks of these viruses from occurring in the first place.

As seen in the COVID-19 pandemic in certain countries such as the U.S., public resistance to health agencies' guidelines and vaccination has resulted in the accentuated spread of SARS-CoV-2. States with lower levels of mask adherence before the relaxation of CDC guidelines were associated with high COVID-19 case rates in the following month, excluding other factors (Fischer *et al.* 2021). Regions in the U.S. that are less

likely to mask or get vaccinated against the virus are more likely to be rural regions, which are already more at risk for COVID-19 due to other factors (Callaghan *et al.* 2021; Centers for Disease Control and Prevention (CDC) 2021c; Texas A&M University 2021). Relatedly, in many states and presumably beyond, rural counties were associated with higher COVID-19 case rates and mortality rates (Huang*et al.* 2021). This association between the willingness to follow CDC guidelines and regulations surrounding COVID-19 and the rate or severity of COVID-19 suggests that increased scientific literacy and boosted public awareness campaigns surrounding pandemics and viral diseases might assist in preventing viral spread within the general population.

The consistent funding for research on human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) has resulted in the development of a plethora of antiviral drugs of different classes that can be used in combination to stave off illness from a disease that was once a death sentence. This is one of the few examples of a virus that has received consistent attention since it began a pandemic in the 1980s that continues today, and one of the few true success stories in conquering a dangerous viral illness in modern history through antiviral drug development. Having effective treatments for a viral disease, be it preventative care or post-symptomatic treatment, completely changes the course of the epidemic.

For most of the viruses mentioned in this paper, there are no available antiviral treatments or vaccines (**Table 5)** . Likewise, there is no consistent funding for these diseases, especially those with high potential to cause disease (such as the Oropouche and Mayaro viruses) but have yet to cause widespread, global outbreaks. Interest in these viruses should not wane past the point where a particular epidemic ends, but more than often, this is the case; as public interest wanes in major epidemic viruses, so does the funding for research into said virus (Bobrowski *et al.* 2020). Both the rapidity and bulk of immediate responses to temporal viral epidemics are typically insufficient to result in a tangible outcome (i.e., vaccine or antiviral medication) past the point the epidemic has ended. EBOV and ZIKV, both described in this paper as being high-risk viruses for future outbreaks, have seen decreased NIH funding available after their initial outbreaks (2014-2016). This decrease in funding is also associated with a decrease in publications associated with these viruses in PubMed (Bobrowski*et al.* 2020). Therefore, it is necessary to maintain interest in these viruses past the point at which they cease to be a problem; just because one epidemic has ended does not mean another will not begin soon after, as with the more recent outbreak of EBOV (2018-2020).

Table 5. Examples of drugs and vaccines that are approved, in development, or may be repurposed against future viral outbreaks.

Virus	**Approved Vaccines**	**Vaccine Development**	**Approved Drugs**	**Repurposed Drugs**
SARS-CoV-2	Pfizer-BioNTech (Comirnaty), Janssen (J&J), Moderna (Spikevax) (COVID-19 Vaccines | FDA 2022)	Many, see ref. (Li *et al.* 2020)	Remdesivir, Paxlovid (EUA), Molnupiravir (EUA) (Melo-Filho *et al.* 2022)	Galdesivir, Remdesivir, Penciclovir, Disulfiram, Lopinavir, Boceprevir (Melo-Filho *et al.* 2022)
SARS-CoV		Inactivated SARS-CoV vaccine (ISCV), VRC-SRSDNA015-00-VP (Li *et al.* 2020)		Galdesivir, Remdesivir, Penciclovir, Disulfiram, Lopinavir, Boceprevir (Melo-Filho *et al.* 2022)

Virus	Approved Vaccines	Vaccine Development	Approved Drugs	Repurposed Drugs
MERS-CoV		ChAdOx1 (Folegatti *et al.* 2020) BVRS-GamVac (Study of Safety and Immunogenicity of BVRS-GamVac - Full Text View - ClinicalTrials.gov 2021) MVA-MERS-S_DF1 (Safety and Immunogenicity of the Candidate Vaccine MVA-MERS-S_DF-1 Against MERS - Full Text View - ClinicalTrials.gov 2021) GLS-5300 (INO-4700) (Safety, Tolerability and Immunogenicity of INO-4700 for MERS-CoV in Healthy Volunteers - Full Text View - ClinicalTrials.gov 2022)		Galdesivir, Ementine, Remdesivir, Disulfiram, Lopinavir, Boceprevir (Melo-Filho *et al.* 2022)
Ebola virus	ERVEBO, Zabdeno/Mvabea (World Health Organization 2020)	ChAd3-EBOZ, Ad5-EBOV, GamEvac-Combi and GamEvacLyo (Woolsey and Geisbert 2021)	Inmazeb, Ebanga (Centers for Disease Control and Prevention (CDC) 2021b)	Miglustat, Clomiphene, Toremifene (Yuan 2015) Tilorone, Quinacrine, Pyronaridine (Puhl *et al.* 2021)
Zika virus		rZIKV/D4Δ30-713, ZPIV (Zika Virus Vaccines | NIH: National Institute of Allergy and Infectious Diseases 2018)		Cilexetil, Auranofin, Bortezomib, Dactinomycin, Ivermectin, Mycophenolic Acid, Thioguanine (Loe, Lee and Chu 2019)
Dengue virus	Dengvaxia (Deng *et al.* 2020)	LATV rDEN4[?]30, TV003/TV005, S16803, EDIII-P64K, V180 (Deng *et al.* 2020)		Nelfinavir, Balapiravir, Mycophenolic acid and ribavirin, ZX-2401, Dasatinib, Ivermectin (Botta *et al.* 2018)

Virus	Approved Vaccines	Vaccine Development	Approved Drugs	Repurposed Drugs
Mayaro virus		ChAdOx1 May (Kroon Campos *et al.* 2020)		EIDD-1931,Favipiravir, Suramin (Langendries *et al.* 2021)
Lassa virus		INO-4500 (Safety, Tolerability and Immunogenicity of INO-4500 in Healthy Volunteers - Full Text View - ClinicalTrials.gov 2020)		Ribavirin, Favipiravir (Rosenke *et al.* 2018)
Norovirus		TAK-214, VXA-NVV-104, Hansenulapolymorpha, Longkoma (Tan 2021)		2'C-methylcytidine, Ribavirin, 2-thiouridine, 5-nitrocytidine, Suramin, Nitazoxanide (Kaufman, Green and Korba 2014)
Influenza virus	Afluria Quadrivalent, Fluarix Quadrivalent, FluLaval Quadrivalent, Fluzone Quadrivalent, Flucelvax Quadrivalent, Flublok Quadrivalent, FluMist Quadrivalent (Centers for Disease Control and Prevention 2019)		Oseltamivir, Zanamivir, Peramivir, Baloxavir marboxil (Centers for Disease Control and Prevention (CDC) 2021a)	Diltiazem (Pizzorno *et al.* 2019)
Nipah virus	rVSV-ΔG-NiVBG (PHV02) (Foster *et al.* 2022)	HeV-sG-V (Foster *et al.* 2022)		
Hanta virus	Hantavax (Liu *et al.* 2020)	pWRG/HTN-M(x) (Liu *et al.* 2020)		Ribavirin, Chloroquine (Vergote *et al.* 2021)

Virus	Approved Vaccines	Vaccine Development	Approved Drugs	Repurposed Drugs
Oropouche virus				Favipiravir (Files *et al.* 2022)
Marburg virus		VSV-MARV (Marzi *et al.* 2021)		Tilorone, Quinacrine, Pyronaridine (Puhl *et al.* 2021)

For decades, most antiviral research followed the "one bug, one drug" paradigm, but with a recent paradigm shift toward broad spectrum drugs, it is unclear how many existing compounds are active against multiple viruses. An open-access small molecule antiviral compound collection (SMACC) was recently developed (Martin *et al.* 2022) to support the discovery of broad-spectrum antiviral drug molecules; currently, it contains over 32,500 chemical bioactivity entries for 13 viruses with high pandemic potential. Their analysis revealed several compounds with multi-viral activity which demonstrated their existence but underscored the need for systematic efforts towards broad-spectrum antiviral discovery, like the Rapidly Emerging Antiviral Drug Development Initiative (READDI) at UNC-Chapel Hill (The University of North Carolina at Chapel Hill). Current research indicates the conservation of viral proteins (Melo-Filho *et al.* 2022) or other conserved viral mechanisms, like involvement of common host factors (Kumar *et al.*2020), could be the key to broad-spectrum antiviral discovery. Obviously, host targets responsible for viral entry should not be forgotten as well (Hochuli *et al.* 2022).

Ultimately, as a society, we should focus more on the future, particularly on how the past informs that future. Anyone alive today can say it is infinitely better not to experience a viral pandemic than to live through the associated economic, mental, and personal tragedies associated with it. All the viruses mentioned– SARS-CoV-2, MERS-CoV, DENV, ZIKV, MAYV, LASV, noroviruses, influenza, Nipah virus, hantaviruses, Oropouche virus, MARV, and Ebola virus– have epidemic potential and require attention to avoid becoming catastrophes. Predictive models are available for some of the diseases and can advise us on when, where, or what strain of virus may emerge. Consistent investment in research and public literacy in science is integral to implementing actual policies that can affect individual lives. If public health officials and politicians worldwide heed the warnings of virologists and data scientists who predict and generate data, they could prevent the next viral epidemic and avoiding mass morbidity and mortality. History sets a precedent for successes and failures, and the handling of many major pandemics in the past are failures. However, this does not have to be the case in the future. We have been warned of the dangers of currently circulating virus strains that exist and their potential for disease. What remains to be answered is whether we will act on these warnings or let them sit stagnant until they putrefy at our feet.

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Conflicts of Interest

AT and ENM are co-founders of Predictive, LLC, which develops computational methodologies and software for toxicity prediction. All other authors declare they have nothing to disclose.

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