

# While We Endure This Pandemic, What New Respiratory Virus Threats Are We Missing?

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In this paper, we review recent human respiratory virus epidemics, their zoonotic nature, and our current inability to identify future prepandemic threats. We propose a cost-efficient, One Health surveillance strategy that will be more efficient and more sustainable than previous efforts.

**Keywords.** emerging respiratory viruses; adenoviruses; coronaviruses; influenza viruses; enteroviruses.

The coronavirus disease 2019 (COVID-19) pandemic has preoccupied health care and public health professionals for more than a year. We are assured that the future holds new emergent respiratory virus threats that could be equally devastating. What virus types should we anticipate? Where do we conduct surveillance for them? How do we better mitigate such prepandemic threats before they cause worldwide morbidity?

## Spillover and Emergence of New Threats

In addition to the widely recognized novel influenza A and coronavirus threats, other respiratory viruses have epidemic if not pandemic potential. These include human metapneumovirus [1, 2], human respirovirus 3 (formerly parainfluenza virus 3) [1], rhinovirus C [3], respiratory syncytial virus, and multiple human adenovirus species [4]. Many of these threats are now recognized as zoonotic (here we equate anthroponosis or reverse zoonosis with zooanthroponosis because zoonoses are often recognized as bidirectional).

The zoonotic nature of some of these viruses was not always appreciated. Human respirovirus 3 and human rhinovirus 3 had not previously been thought to be zoonotic. Cross-species

spillovers of metapneumovirus [5] and adenoviruses [6] have been previously postulated, but until recently [1, 2] were largely discounted [7, 8]. There is growing evidence that adenoviruses [9] and enteroviruses [10] are, at least occasionally, jumping species. The zoonotic nature of such pathogens matters because the viruses responsible for the 2009 H1N1 pandemic and the current COVID-19 pandemic came from animals and have both abjectly surprised public health officials with their rapid spread and high morbidity. We argue that their emergence was not expected because sparse surveillance was being performed at the human–animal interface.

## Novel Respiratory Viruses' Impact on Humans

The impact of novel respiratory virus infections in humans is not trivial (Figure 1). Between 2002 and 2004, severe acute respiratory syndrome coronavirus (SARS-CoV) emerged in China and rapidly spread to 29 countries before it was controlled with aggressive public health and hospital infection control measures. In 2006, a novel human adenovirus 14 strain (Ad14) emerged in the United States and spread to other countries, causing at least 1000 illnesses and 13 deaths. While surveillance for this “killer cold virus” is sparse, available data suggest that it spread to at least Ireland, Canada, and China and still circulates today. In 2009, a triple reassortant H1N1 swine-like influenza virus emerged in Mexico and quickly spread throughout the world, causing an estimated 60.8 million illnesses and 12 469 deaths in the United States alone [11]. This deadly influenza strain continues to circulate today. In 1969, enterovirus A71 (EV-A71) was first isolated in California, with outbreaks from 1972 to 1990 identified in 6 countries [12]. In the Asian-Pacific region, EV-A71 became endemic in the 1990s, affecting thousands of children to manifest what is recognized as hand, foot, and mouth disease [12]. While surveillance is still sparse, the virus has caused at least 12.8M infections and 3747 deaths in Asia alone, with major outbreaks continuing to occur every 3–4 years [12]. Enterovirus D68 was first isolated in California in 1962, and since then, there have been infrequent cases in the United States and minor outbreaks in Europe, Africa, and Southeast Asia. In 2014, a novel clade of a second enterovirus, D68 (EV-D68), was implicated in a series of outbreaks of respiratory disease in 21 countries. There were at least 2287 EV-D68 illnesses and 17 deaths attributed to this virus [13]. The virus has also caused outbreaks of severe respiratory disease in Asia and was recently implicated as the cause of acute flaccid myelitis [14].

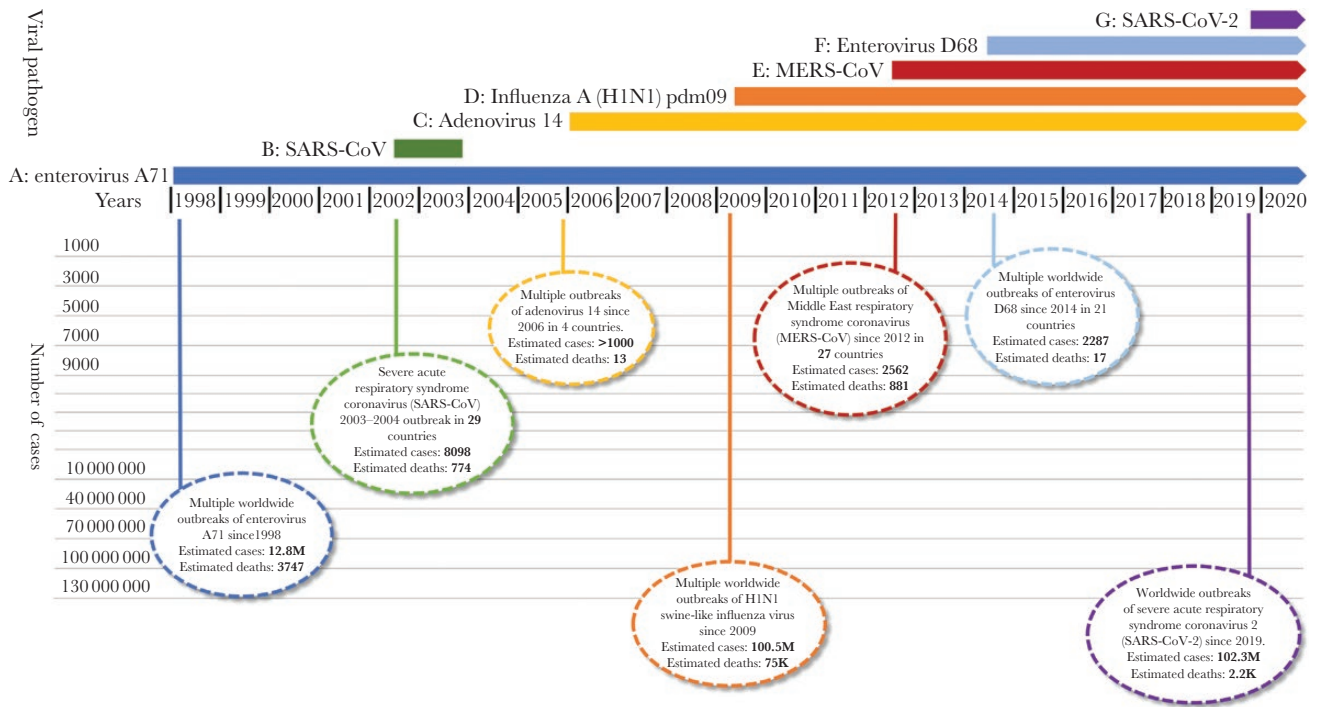
It is unfortunate that our public health response to recent emergent novel pathogen events has largely been transient. Former Centers for Disease Control and Prevention Director Julie Gerberding, MD, addressed this concern in her November

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**Figure 1.** Recent outbreaks of emerging respiratory viruses in humans. A, Enterovirus A71 worldwide outbreak. Presented cases are from the Asian-Pacific region only, 1998–2018 [12]. B, Severe acute respiratory syndrome coronavirus (SARS-CoV) November 2002–July 2003 outbreak. This virus is zoonotic in origin [15]. C, Adenovirus 14 multiple outbreaks [16]. D, Influenza A (H1N1) pdm09 virus. Presented cases are for the years 2009–2018. This virus is zoonotic in origin [11]. E, Middle East respiratory syndrome coronavirus. Presented cases include data from September 2012 to November 2020. This virus is thought to be of zoonotic origin [17]. F, Enterovirus D68 multiple outbreaks. Cases presented here are for 2014–2015 [13]. G, Severe acute respiratory syndrome coronavirus 2 pandemic. Cases presented here are counted through January 2021. This virus is zoonotic in origin [18].

2019 testimony [19] before the US Senate Armed Services Hearing:

When health crises strike—measles, MERS, Zika, dengue, Ebola, pandemic flu—the American people grow alarmed and U.S. policymakers spring into action, rushing to allocate resources in response. Yet all too often, when the crisis fades and public attention subsides, urgency morphs into complacency. Investments dry up, attention shifts, and a false sense of security takes hold.

#### Novel Respiratory Viruses Also Threaten Domestic Animals and Wildlife

Novel respiratory pathogens are not only emerging among humans, but also among animals. The livestock–wildlife interface has played an important role in the spillover and the virulence of viral pathogens. For instance, transmission of avian influenza viruses from migratory aquatic birds to domestic poultry has been commonly reported. In addition, new threats of reverse spillover have recently been identified. Surveillance of avian respiratory viruses in wild birds indicates the spillover of mutant viral vaccine strains avian paramyxovirus serotype 1 (APMV1) and avian coronaviruses (ACoV) from commercial poultry to wild birds. These strains have an enhanced ability to transmit across species [20]. Interactions between humans,

domestic animals, and wildlife create inevitable opportunities for the emergence of novel strains.

#### Economic Burden of Novel Respiratory Viruses

Beyond causing high morbidity and mortality, emerging respiratory viruses have also had major impacts upon international travel, trade, and economies. In a 2018 report [21], The World Bank estimated that the SARS epidemic cost the affected nations US\$30–50 billion, and the H1N1 pandemic US\$45–55 billion. An incursion of MERS-CoV in South Korea during June 2015–June 2016 was estimated to cost that nation US\$2.6 billion [22]. At this juncture, it is clear that the economic impact of COVID-19 will exceed all recent respiratory disease outbreaks.

#### Where and How Should We Conduct Surveillance for Novel Respiratory Viruses

Most of these novel emergent respiratory viruses come from 4 different viral families (*Coronaviridae*, *Adenoviridae*, *Orthomyxoviridae*, and *Picornaviridae*) and are thought to have originated in animals before crossing over to infect humans. Epidemiologists, ecologists, and modelers have attempted to predict novel pathogen emergence. Studies have been conducted to identify risk factors associated with emerging influenza A viruses [23], emerging infectious

diseases [24], and emerging zoonotic diseases [25]. The identified risk factors for specific viruses are complex and sometimes disparate. However, these factors often point to densely populated geographical areas in Asia as areas of high emerging infectious disease risk. They also point to encounters with live animals, especially around markets where animals are sold [26, 27], as a source of virus mixing and human infection risk.

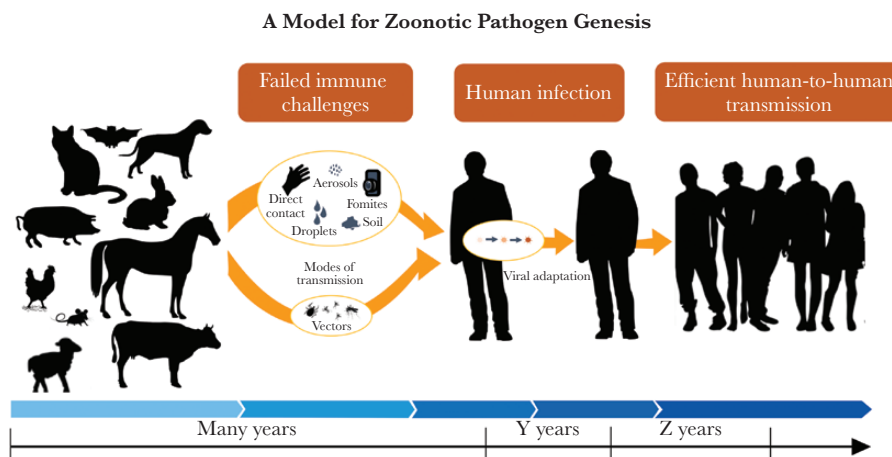
The time and process for viruses to transition or adapt from an animal virus to a human zoonotic pathogen are unknown, but it seems logical that it takes many years and varies with each zoonotic pathogen (Figure 2). For instance, viral evolutionary data suggest that the coronavirus lineage giving rise to SARS-CoV-2 departed from the nearest similar virus in bats after ~1969 [28]. While the virus likely circulated in bats or in an intermediate animal host during some of this time, it seems likely that the virus took quite some time in adapting to humans and longer still to become the pathogen we face today. These long transition periods provide an important opportunity to mitigate novel respiratory virus threats before they fully adapt to humans and become highly transmissible.

If we focus novel pathogen surveillance at the human–animal nexus (Figure 2), we are likely to be more efficient in detecting pathogens that threaten humans, as compared with other more ambitious surveillance strategies that focus upon the comprehensive study of all the viruses that reside in the world’s animals. In embracing the latter approach, programs such as USAID’s PREDICT I and II programs and the new Global Virome Project have been criticized as expensive and not likely to find pathogens that will be human threats. Their previous costs (PREDICT >\$169M since 2009), future proposed costs (Global

Virome Project \$3.4B), and ambitious plans have been questioned [29–33]. Similarly, leaders at the US National Institute of Allergy and Infectious Diseases have proposed 20 years of large human cohort studies and intensive immunology and pathology research involving 120 pathogen groups [34–36], yet they freely admit that the associated cost is prohibitive [34].

There is a growing demand for innovative and cost-effective approaches to surveil for the next novel respiratory virus threat. We need to mitigate novel respiratory virus threats before they fully adapt to humans and become highly transmissible. The most strategic approach would be directing periodic, novel respiratory virus surveillance at the human–animal interface, studying both animal workers and their animals [37]. Alternatively, if surveillance cannot be conducted at the human–animal interface, surveillance for novel respiratory viruses among human pneumonia patients should be conducted in geographical areas known to be at high risk of novel respiratory virus emergence. We have recently used these methods and found evidence of novel zoonotic coronaviruses among humans hospitalized with pneumonia [38], a zoonotic adenovirus infection in a patient with respiratory illness [39], evidence of human enteroviruses in pigs [39], and first evidence of influenza D virus in poultry [40]. We have found success through conducting monthly periodic surveillance both in live animal environments (industrialized farms, live animal markets, etc.) and among pneumonia patients in large hospitals for about \$25 000 per year per site.

To conduct such effective surveillance, developed countries need to rethink current global security strategies and form better global health partnerships, embracing the interdisciplinary One Health approach to novel respiratory virus



**Figure 2.** Here we illustrate how a animal pathogen may become a zoonotic human pathogen. Evolutionary studies suggest that such viral adaption to man is a progression of events, each step of which that may take multiple years. Illustration by Emily Robie, images from publicdomainvectors.org. Adapted from Dr. V. Stalin Raj’s graphic: [http://www.iisertvm.ac.in/faculty/stalin/research\\_areas?%2Ffaculties%2Fstalin%2Fresearch\\_areas=](http://www.iisertvm.ac.in/faculty/stalin/research_areas?%2Ffaculties%2Fstalin%2Fresearch_areas=).

surveillance. Surveillance at the human–animal nexus is likely to be better focused and less expensive than some of the other strategies currently being contemplated.

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**Author contributions.** G.C.G. conceived the idea and drafted the manuscript. A.A. assisted in drafting the manuscript. Both authors approved this article for publication.

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