From "A"IV to "Z"IKV: Attacks from Emerging and Re-emerging Pathogens

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100 years after the infamous "Spanish flu" pandemic, the 2017–2018 flu season has been severe, with numerous infections worldwide. In between, there have been continuous, relentless attacks from (re-)emerging viruses. To fully understand viral pathogenesis and develop effective medical countermeasures, we must strengthen current surveillance and basic research efforts.

This year marks the centenary of the "Spanish flu" pandemic, the most devastating viral pandemic in history caused by an H1N1 influenza A virus that infected over 500 million and killed between 50 and 100 million people. We know to expect a flu season every year; the question is always how severe it will be. With high numbers of influenza infections reported worldwide during this season, we are again reminded of the public health threat stemming from a potential influenza pandemic. The US Centers for Disease Control and Prevention (CDC) reported that this is the first time in the past 15 years that all states in the entire continental USA have reported widespread flu activity during the same week. In China, the reported number of flu cases have increased over 2-fold compared to the flu seasons in the past several years—the second-highest recorded number, just after the 2009 pandemic H1N1 (pH1N1)—and many patients have been hospitalized with severe clinical symptoms. These events have raised concerns that we are in danger of another flu pandemic. Circulating flu viruses are quite diverse this year—including the "swine flu" 2009-pH1N1, H3N2, and influenza B/Victoria and B/Yamagata—and are spread across various geographical locations. The H3N2 subtype is dominant in the UK and the USA, but a mixed pool of pH1N1, H3N2, and influenza B/Yamagata, with a small portion of B/Victoria, have been reported in China. A universal influenza vaccine to combat such mutation-prone viruses is urgently needed yet still far from reach, despite the global efforts. Despite best efforts to anticipate the emergent strains, vaccines vary from year to year in terms of efficacy, with this year's providing only moderate protection.

Human infections with different subtypes of avian influenza A viruses (AIVs) have been consistently reported since H5N1 AIV was reported in Hong Kong during 1997 (Yuen et al., 1998). Infections with AIV typically result in high case fatality rates (CFRs) ranging from ~30% to ~70%, and at least 14 influenza A virus subtypes—including the three seasonal flu viruses, H1N1, H2N2, and H3N2—have reportedly infected humans to date (Figure 1). Of note, influenza A virus has a segmented genome with 8 genomic segments encoding at least 10–16 proteins, two of which are hemagglutinin (HA) and neuraminidase (NA). There are currently 16 (+2) HA genes and 9 (+2) NA genes (+2 means two more HA or NA from bat-derived influenza-like viruses, for which only genomic sequences are available, but no alive virus has yet been isolated; Wu et al., 2014). The combination of HA and NA would theoretically yield 144 subtypes of HxNy viruses. Due to the migratory birds' travel and live poultry trade, which includes the transport of poultry and operation of live poultry markets (LPMs) throughout China and Southeast Asia (Gao, 2014), we should expect more human infections with AIVs in the future. AIVs may supply genomic segments for reassortment with circulating seasonal influenza viruses to generate a novel pathogen with high CFR and pandemic potential. As we can't yet eradicate seasonal flu, efforts to change the traditional live poultry trade—for example, the traditional LPMs—in order to restrict the flow of domestic poultry migration may help decrease the probability of the emergence of novel AIV subtypes, even the potential pandemic viruses.

Flu isn't alone. Coronavirus is another family of emerging pathogens with public health concern. A devastating but quickly conquered outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV) during 2003 transformed China's approach to outbreak control. A sophisticated surveillance system has since been put into place. While primarily government led, there is extensive collaboration with various institutes in the academic, industry, and healthcare fields to produce a wide-ranging, comprehensive network that issues warnings of an impending outbreak at the earliest opportunity. As exemplified by the Chinese Academy of Sciences Center for Influenza Research and Early-warning (CASCIRE) network, in addition to Chinese National Influenza Center/WHO Collaborating Center for Reference and Research on Influenza under China CDC, such a system can drive basic, applied, and translational research on infectious disease control and prevention (Bi et al., 2017). A related coronavirus, the Middle East respiratory syndrome coronavirus (MERS-CoV), emerged in the Middle East during 2012 and has on occasion caused sporadic infections with imported cases from returning travelers, some of which go on to infect others. One such instance was the importation of a MERS-CoV case into China from South Korea during 2015 (Su et al., 2015), in which the traveler was promptly
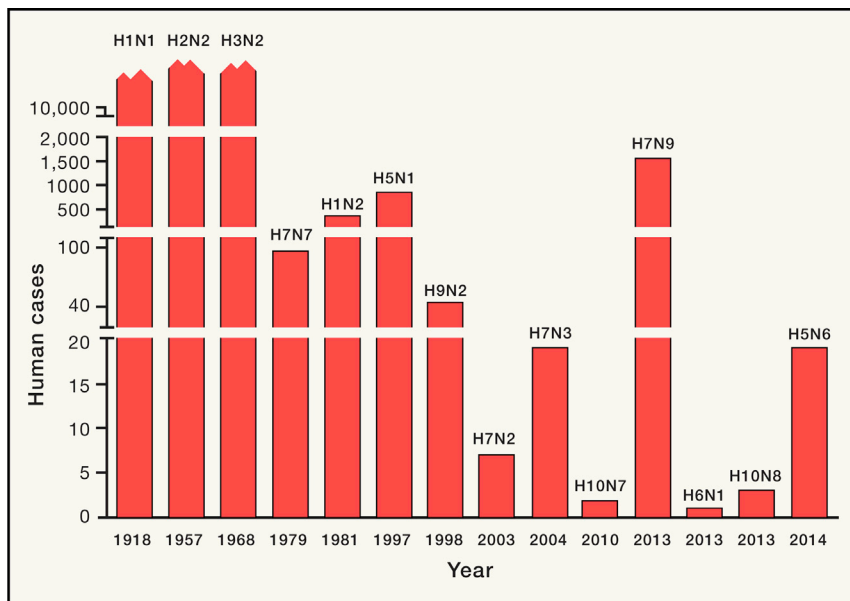
Figure 1. Human Infections with Subtypes of Influenza A Viruses
The numbers of human cases infected by different subtypes of influenza A virus reported worldwide are shown in histogram (WHO, 2017a). The x axis presents the time points (year) of the first reported case for each subtype virus. The y axis presents the total numbers of reported human cases to date. The case numbers of human-infecting H1N1, H2N2, and H3N2 are extraordinarily large and are not available for exact counts due to influenza pandemics such as the 1918 H1N1 Spanish flu, 1957 H2N2 Asian flu, and 1968 H3N2 Hong Kong flu.

identified and quarantined, preventing further infections. Due to the ongoing nature of the MERS-CoV outbreak, we are likely to encounter more coronavirus infections in the future. Preparations should be made accordingly through the development of both vaccines and antivirals.

Ebola virus (EBOV), first identified in Central Africa during 1976, unexpectedly struck West Africa during 2013–2015, impacting several countries in North America, Europe, and Africa. After earlier incidents, efforts were underway to develop vaccine candidates; however, these were challenged, as the virus was at first suspected to have a higher mutation rate that might negatively impact the efficacy of the EBOV vaccine candidates under clinical trials (Gire et al., 2014). To address this question directly, a total of 175 whole-genome sequences were obtained from viral isolates, and the mutation rate was determined to be similar to that of past EBOV outbreaks (Tong et al., 2015). Therefore, current experimental vaccines should still be efficacious. During this epidemic, application of genomic sequencing technology greatly facilitated disease control. Molecular epidemiology

and pathogenesis studies, in addition to the development of effective antivirals, such as the ZMapp antibody cocktail and the vesicular-stomatitis-virus (VSV)- and adenovirus (Ad5, chAd3)-based vaccines, were the key measures for the effective control of these pathogens.

While the world was still celebrating the success of finally conquering EBOV after a protracted 2-year battle, Zika virus (ZIKV) struck with the first cases reported in Brazil after small outbreaks previously reported in Micronesia (Yap Island) and French Polynesia in 2007 and 2013, respectively (Figure 2). As an obscure pathogen (but known to humans since 1947), the ZIKV isolates from the 2015– 2016 epidemic were found to possess new characteristics (Grubaugh et al., 2018). The virus quickly spread geographically with at least 84 countries/regions affected (Figure 2). A coordinated global response eventually led to the conclusion of the epidemic in November 2016, but long-term complications stemming from ZIKV infections are yet being reported from convalescent patients.

After the ZIKV epidemic, outbreaks of yellow fever virus (YFV) occurred across

Angola and Brazil in 2017. The virus was imported to China as Chinese workers returned from Angola (Chen et al., 2016). Almost simultaneously, Rift Valley fever virus (RVFV) was also imported into China from Angola through a returning traveler. These events highlighted the difficulty in accurately predicting the time and location, as well as the identity, of the causative pathogen behind the next outbreak. Indeed, EBOV and ZIKV were both considered neglected, tropical re-emerging pathogens, SARS-CoV and MERS-CoV were novel, emerging pathogens, and influenza viruses were typically re-emerging pathogens with new properties derived from genetic evolution and reassortments.

A myriad of contributing factors such as urbanization, globalization, and climate change will impact the pathogenicity and transmission of certain pathogens, as well as the distribution of their reservoir hosts. This reality places additional emphasis on the importance of proactive countermeasures, such as pathogen surveillance and vaccine development, as well as the need for reactive countermeasures, such as antiviral therapy.

As a community of scientists, clinicians, public health experts, and caregivers, we have so far been able to answer the challenges posed by a spectrum of pathogens ranging from "A"vian influenza virus to "Z"ika virus. Each has taken time and a somewhat tailored approach. We can expect sterner tests in the future, and some of the lessons learned must be carried forward. Since the spread of (re-)emerging viruses is not confined by geographic boundaries, it is clear that collaborative solutions across nations are needed to solve these global problems. Efforts in this vein are getting off the ground. International partnerships, such as the Global Virome Project (Carroll et al., 2018) for virus hunting worldwide and the establishment of a CDC network in Africa with assistance from the US CDC and China CDC, will greatly improve our capacity for surveillance, contributing to, ideally, a worldwide system in the "big data" era of the 21st century. The Pandemic Emergency Financing Facility (PEF), launched by the World Bank in collaboration with the World Health Organization and the governments of Japan and Germany, aims to provide
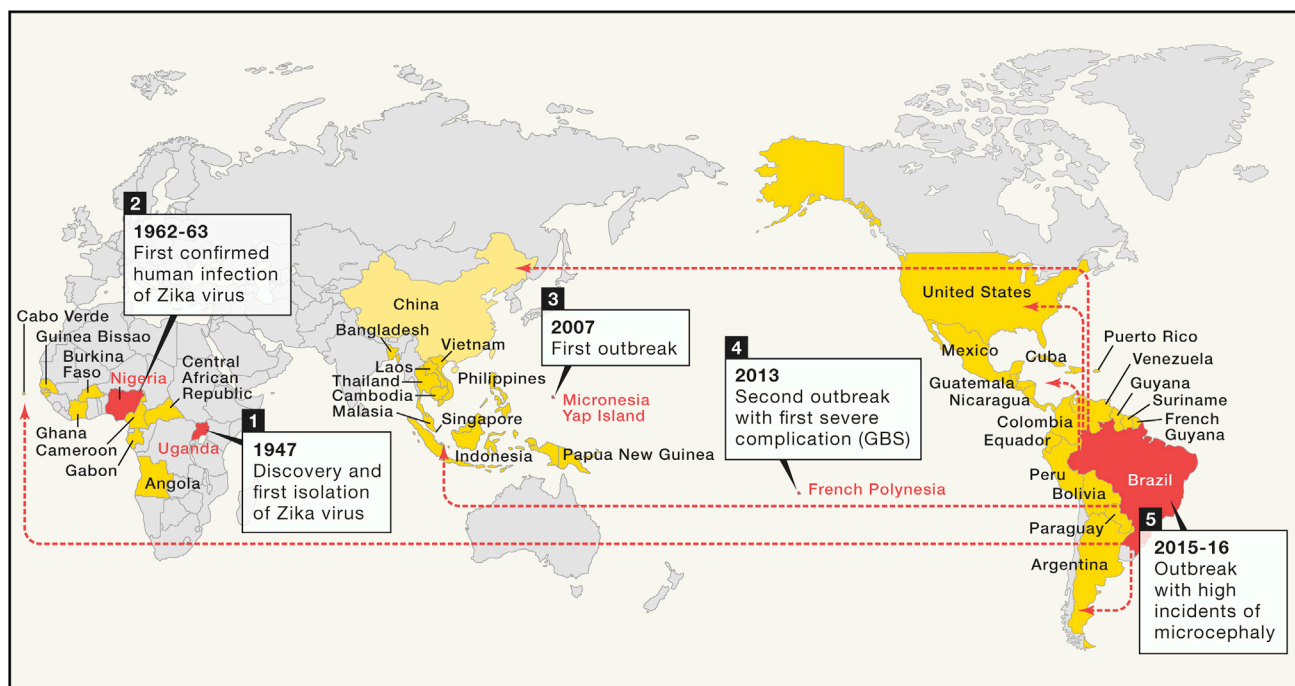
Figure 2. Geographical Distribution of Zika Virus Infections, Addressing the Spread of the 2015 Brazil Outbreak
Locations where big events of Zika virus infection occurred were indicated in red. These events are described in boxes and numbered according to the time sequence. The dashed arrow lines represent the spreading routes of Zika virus during the 2015–2016 outbreak. Regions with evidence of Zika virus transmission are colored in yellow, except for the five red-colored ones as mentioned above. China is colored in light yellow due to the imported cases in 2016 and the isolation of Zika virus in local vector, although not in the 84 countries with Zika virus transmission according to the WHO classification (WHO, 2017b).

over $500 million to cover developing countries against the risk of outbreaks. The Coalition for Epidemic Preparedness Innovations (CEPI), founded by the Norway government, the Bill & Melinda Gates Foundation, the Wellcome Trust, and the World Economic Forum aim to provide a coordinated, bench-to-bedside approach for (pre-)clinical vaccine development and delivery. The above examples show that we are beginning to learn our lessons, but we must not forget that basic scientific research into both high-profile and obscure pathogens forms a crucial basis for the effective implementation of informed public health policies and innovative collaborative initiatives. Robust investment into basic research (i.e., viral pathogenesis, interspecies transmission, etc.) should be encouraged to achieve a fully multi-faceted approach to combating future pandemics.

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