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Editorial

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Viruses without Borders: Deadly Outbreaks of the 21st Century

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Rapid trends in globalization, increase in population, and genetic diversity of viruses collectively provide grounds for emergence and reemergence of viral outbreaks that are threats to overall continuum of human development. In addition to human factors, environmental factors such as water, soil, mosquito vectors and animals are also contributing to the outbreaks of viral diseases. In the past two decades, we have witnessed some of the deadly viral epidemics of the 21st century such as the Ebola virus epidemic in West Africa [1], Yellow Fever outbreak in Angola [2], the 2009 flu pandemic [3]. Dengue Fever [4], and Zika outbreak especially in Brazil [5], just a few to mention. From such outbreaks occurring unpredictably around the world, infectious diseases epidemiologists and global health experts acknowledge viruses have now evolved to rapidly cross international borders. In countries where resources of rapid viral detection and prevention programs are indeed limited, these outbreaks have produced devastating consequences not only overwhelming the local health departments' capacity to confront the epidemics, but also, they have had serious and measurable devastating effects on economy and human productivity [6].

In 2014, the world health community witnessed an outbreak of Ebola in West Africa, primarily in Liberia, Sierra Leon and Guinea. The virus took the lives of more than 11,000 people in these countries. The impact of the outbreak was so devastating that the World Health Organization (WHO) was subject to criticism among healthcare experts [7]. Now, the current leadership of the WHO is committed to implementing targeted action plans along with assisting nations in providing early warning signs, healthcare delivery capacity-building, technical assistance, and resource mobilization. Recovery from Ebola is dependent on early disease onset, adequate supportive care, and the patient's immune system. People who recover from Ebola infection develop antibodies that last for at least 10 years (Source: WHO). In addition, novel preventive public health measures such as vaccine development became available which has been shown to be effective in limited trials during the outbreak in West Africa [8]. The virus causes internal hemorrhage and has a remarkable capability to rapidly spread through contact with a miniscule amount of bodily fluid. In Congo, the epidemic was often transmitted to humans by contact with an infected animal. Ebola continues to be a threat - the virus has killed 26 people in a deadly recent epidemic in the Democratic Republic of Congo [9]. However, as the global level of the threat was not determined to be high, the WHO did not declare a global health emergency response with respect to Congo's recent outbreak.

The Yellow Fever outbreak caught the attention of the WHO and CDC on January 21, 2016. The national health authorities of Angola notified an outbreak of a mosquito-borne virus, the first case was initially identified with the onset date of December 5, 2105, which was then detected in Vaina municipality of the Luanda province. As of May 20, 2016, a total of 2420 suspected cases, including 298 deaths, had been reported [10]. In collaboration with the WHO, the government of Angola initiated an immunization program starting in Viana municipality and subsequently covering at least 7 provinces of Angola that were at the risk of outbreak. During spring of 2016, International Coordinating Group (ICG) for Vaccine Provision delivered almost 1.9 million vaccines which were then complemented by activities such as social mobilization, radio and TV to effectively bring awareness among the public for Yellow Fever vaccination campaign specifically in the district of Luanda. The epidemic in Africa had generated concerns among global health experts for the containment of Yellow Fever and the virus quickly mobilized itself from the initial site of the outbreak and spread to Democratic Republic of Congo, Kenya and China (crossing the continent) by way of travelers [10]. The immediate concern was about the travelers who did not have vaccination against the virus posing both vulnerability and possibly serving as reservoir career to spread infection.

Influenza outbreaks take place during the winter months. The virus has genetically evolved to continuously modify itself by what is known to be antigenic shift and drift. In case of antigenic shift, the virus evades immune system [11]. Annual fatality of influenza is well established and elderly are more prone to this virus. Clinical characterization of influenza is well documented in practice of respiratory medicine which is associated with morbidities and mortalities. The first flu pandemic was recognized in 1918 known as the Spanish flu which killed an estimated 50–100 million people worldwide, and has been referred to as "*the mother of all pandemics*" [12]. In the past two decades, the global health community at large has witnessed two major deadly outbreaks namely the 2005 avian influenza - Bird Flu H5N1 [13], and the H1N1 (Swine flu) pandemic of 2009 [14]. Both H5N1 and H1N1 subtypes are highly contagious. The highly pathogenic avian H5N1 was initially discovered in

South Africa in 1961. Migratory shore birds were determined to be affected by the virus which is often deadly. In 1997, serious illness occurred in Hong Kong and H5N1 was responsible for 18 documented cases of severe respiratory illness with 6 cases of fatalities. The affected individuals were investigated to be in close contact with contaminated poultry. Immunopathogenesis of H5N1, and H1N1 has been attributed to production of specific type of cytokine response which is termed cytokine storm with significant mortality [14]. The H1N1 pandemic occurred on June 2009. WHO declared a global pandemic of a novel influenza A, H1N1, which raised the awareness of the health departments worldwide reaching a pandemic level of Phase 6 [15]. Subsequently, more than 70 countries had acknowledged the cases of H1N1 infection. Since then, the virus continued to spread worldwide including detection of novel cases of H1N1 in the United States which was recorded to be a large outbreak internationally. However, most people who had become ill recovered without requiring significant medical care attention. The H1N1 in conjunction with regular seasonal flu may yet pose for significant risk of hospitalization and deaths especially in resource-limited countries. One of the most important lessons of H1N1's pandemic was its impact on the healthcare system. There is general consensus worldwide that it caused the signs of stress in the developing countries, and in resource-limited countries, it overwhelmed the healthcare system especially the intensive care units (ICUs).

Another global public health concern is dengue virus which is an acute febrile illness and transmitted by mosquitoes of the genus *Aedes*. This virus was discovered in 1943 by two Japanese scientists in Nagasaki. It is an old virus that has reemerged during the latter half of the 20th century. The infection primarily is caused by four serotypes; DEN-1, DEN-2, DEN3, and DEN-4. All serotypes can be found worldwide. It is a major health issue throughout the tropics and subtropics with more than 100 countries at risk of endemic. Dengue is an important arthropod-borne (arbovirus) illness in humans [16]. The incidence of dengue has increased dramatically in the recent years. There are more than 50 million cases occurring annually. Nearly 40% of the world's population is at risk of dengue virus transmission [17]. In some individuals who have developed infection with one dengue serotype, they may develop bleeding and endothelial leak upon infection with another dengue serotype which is termed dengue hemorrhagic fever as well as dengue shock syndrome [18]. Dengue fever is typically self-limited with a mortality rate of less than 1%. The treated cases have a mortality rate of 2-5%. In contrast, the mortality rate in untreated cases is as high as 20%. In the viremic phase, dengue virus becomes a blood-borne infection, which can also be transmitted from mother to fetus in utero or to infants at the delivery – perinatal transmission [19].

The CDC reports that cases of dengue in returning US travelers have increased during the past 20 years. According to the CDC, dengue has become the leading cause of acute febrile illness in US travelers retuning from the Caribbean, South America, and Asia. One of the largest outbreaks in past two decades occurred in 2018 in Thailand with 126 fatalities [20]. Thailand also recorded its worst dengue epidemic in 1987 with 174,000 infected cases and with a fatality of 1,007. The lack of selective antiviral agents and an effective vaccine results in approximately 500,000 affected individuals, mainly children, being hospitalized each year throughout the world let alone dengue produces significant economic losses for both households and whole nations. Recently, a dengue virus vaccine has been in use in some countries, but the use is designed for those living in endemic areas for many years that have also developed multiple infections. Such a vaccine currently is not recommended for travelers (Source: CDC Office of Medical Services, Division of Infectious Diseases – Tropical Medicine).

A virus that has recently reemerged and crossed international boundaries is Zika virus. Like dengue, this virus is a member of the arbovirus family. Zika virus was first recorded in a febrile rhesus monley in the Zika forest of Entebbe, Uganda. Shortly thereafter, it was reported in a field worker [21]. Zika is known to widely cross international boundaries outside Africa. Zika epidemics have also been described in Micronesia and French Polynesia [22]. The transmission to human takes place through the bite of an infected *Aedesaegypti* mosquito. In 2015, the outbreak of this virus was reported in Brazil. The illness was characterized by skin rash and absent or low grade (short-term) fever. Based upon clinical presentation, it was challenging to diagnose Zika from dengue or Chikungunya virus. Brazil has also experienced epidemics of Chikungunya virus [23]. Because of the mild nature of the disease, more than 80% if Zika virus infection cases likely go unnoticed [24]. Zika maculopapular rash is the predominant presenting symptom which is likely immune-mediated involving the face, trunk, and extremities, including palms and soles [25]. In few affected individuals, Zika virus can cause neurological complications such as Guillain-Barre syndrome [26]. Of greatest clinical concern over the complications of Zika virus infection is congenital malformations which are primarily due to transplacental transmission of the virus causing microcephalic complications [27]. In January 2016, it was reported the number of babies born with suspected microcephaly reached nearly 4,000 in Brazil (Source: BBC News, January 21, 2016). Because both dengue and Zika epidemics occurred in Brazil (and in other Latin American countries), a new study showed prior dengue infection may protect against symptomatic Zika in children [28]. The epidemics of Zika in Brazil challenged the country's healthcare delivery system. Although the epidemic of Zika in Brazil subsided, there are questions about an effective epidemiological surveillance as well as socio-economic impacts and public health gaps that the virus left behand. The outbreak of 2015-2016 also presented with financial challenges and how complex issue like Zika can be looked at a comprehensive perspective and collaborative efforts of various stakeholders to help address such issues. Zika epidemic of Brazil highlighted an unequal burden on healthcare delivery system.

This editorial sought to explore the current complex challenges that the world's health community may face with respect to outbreaks of deadly viruses – few examples were provided in this editorial. Although tremendous progress has been made in the past years to improve epidemiological surveillance and rapid detection of viruses that cross international borders, yet capacity-building for rapid detection and optimal care delivery are just examples of few obstacles and challenges that global health faces especially in resource-limited countries. The emergence and reemergence of deadly viral outbreaks are major international public health concern. Such issues merit collaborative and decisive local, national and international plan of action. As reemergence of deadly outbreak can take place again, viruses without borders highlighted in this editorial will continue to get the attention of healthcare professionals, international media, infectious diseases epidemiologists, NGOs, and national/international public health sectors. It must be emphasized

while hand washing which is the basic principle of prevention and control, such preventive measure may not be adequate for the spread of deadly viruses in the communities. Consequently, deadly viruses can seriously impact and destroy the lives if not dealt with proper and effective action plan. A "One Health" perspective can help to address these complex issues of preparedness and response [29].

One Health approach is formulated to mitigate and curb public health best practices through its interdisciplinary determinants. One Health concept can also identify environmental factors that help spread the disease outbreak. Major health organizations, such as WHO, CDC, the US Institute of Medicine (IOM) and the European Centers for Disease Control have unanimously concluded more action and information are needed to prevent and control large emerging and reemerging infectious diseases epidemics. A comprehensive framework like One Health approach encompasses a systemic perspective which is fundamental to understand, address, and tackle the consequences of viral epidemics. To meet the global challenges in the context of deadly viral infections, interdisciplinary collaborations facilitate the development of knowledge and establishes scholarly synergism to formulate a comprehensive approach in disease interventional and control policies [30].

Footnote

While in the final preparation stage of this editorial, the author came across with a most recent article from The Lancet entitled "*Venezuela's humanitarian crisis, resurgence of vector-borne diseases, and implications for spillover in the region*" by Maria E Grillet et al. The article is published online on February 21, 2019. Venezuela is currently facing a resurgence in dengue, Zika, Chagas disease and malaria due to its ongoing political and humanitarian crises which have already further compromised it's already existing broken down health system and is seriously threatening its public health infrastructure. The World Health Organization has alarmed the global community that diseases transmitted by insects in Venezuela can lead to a significant loss of life. According to the research article published in The Lancet, the incidence of dengue increased by more than four times from 1990 to 2016. Furthermore, the frequency of Zika outbreaks with epidemic potential appear to be increasing as experts found 2,057 cases of Zika virus per 100,000 people. The high prevalence of such diseases is further compounded by the lack of public health standards, shortage of food, medicine, and vaccine in Venezuela. The crisis in Venezuela exemplifies the need for capacity-building and multispectral approach adapting a One Health strategy to control the spread of insects-borne diseases.

Conflict of Interest Statement: The author declares that the research conducted was in the absence any commercial relationship or financial gain that could be construed as a potential conflict of interest.

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