

# New global viral threats

Hakan Erdem, MD, Serhat Ünal, MD.

## ABSTRACT

لقد أدت الأمراض المعدية إلى كوارث جسيمة في حق البشرية على مر التاريخ مثل ما حدث في القرن الرابع عشر مع اجتياح مرض البُرطان للقارة الأوروبية وقتله لنصف سكان هذه القارة. يعد كلا من فيروس إيبولا وفيروس أنفلونزا الطيور من الفيروسات المسببة للأمراض والمميتة التي نواجهها حالياً في العقد الثاني من القرن الواحد والعشرون. ولقد ظهر فيروس إيبولا في الآونة الأخيرة في القارة الأفريقية، في حين يمكن اعتبار فيروس أنفلونزا الطيور أكثر ظهوراً في آسيا الجنوبية. يهدف هذا المقال إلى دراسة الوضع الراهن فيما يتعلق بالأمراض المعدية، بالإضافة إلى احتمال خطر ظهور أنواع أخرى من الفيروسات المهددة للبشرية في المستقبل

Infectious diseases have caused great catastrophes in human history, as in the example of the plague, which wiped out half of the population in Europe in the 14th century. Ebola virus and H7N9 avian influenza virus are 2 lethal pathogens that we have encountered in the second decade of the 21st century. Ebola infection is currently being seen in West Africa, and H7N9 avian flu appears to have settled in Southeast Asia. This article focuses on the current situation and the future prospects of these potential infectious threats to mankind.

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From the Department of Infectious Diseases and Clinical Microbiology (Erdem), GATA Haydarpaşa Training and Research Hospital, Istanbul, and the Department of Infectious Diseases (Unal), Faculty of Medicine, Hacettepe University, Ankara, Turkey.

Address correspondence and reprint request to: Prof. Dr. Serhat Ünal, Department of Infectious Diseases, Faculty of Medicine, Hacettepe University, Ankara, Turkey. Tel. +90 (312) 3111271. E-mail: sunal@hacettepe.edu.tr / unalserhat57@gmail.com

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Outbreak is an epidemiological definition to describe an unexpected occurrence of an infection at a certain time and place. It may affect a small and a localized group, or impact on millions of people across continents. Two cases of a linked rare infection can be defined as an outbreak. A revisit through the history discloses that outbreaks were vast, deadly, and basically changed the course of human history.<sup>1</sup> As an example, the plague reshaped the landscape of Europe and the world between 1347 and 1351. During this period, the global population was estimated to be 450 million, and 75 million at a minimum are believed to have perished. Consequently, half of Europe died in a period of 4 years.<sup>2</sup> In the pre-antibiotic era, bacterial outbreaks caused much more mass destruction compared with other outbreaks with different infectious agents.<sup>1</sup> But, this trend changed with the advent of antibiotics and viral outbreaks emerged. We believed that Ebola virus and H7N9 avian influenza virus are the most potential pathogens to cause mass destruction in the world. Thus, in this paper, we will focus on the current outbreaks of these 2 viral infections with the potential to cause mass destruction, and to greatly impact the international travelers.

**Ebola hemorrhagic fever.** The *Filoviridae* (Ebola, and Marburg viruses are the commonly known 2 members of *Filoviridae*) were originally documented in 1967 when the apes from Uganda led to outbreaks of hemorrhagic fevers among vaccine plant workers in Germany and Yugoslavia. These workers had direct contact with the animals by killing the apes, removing their kidneys, or preparing cell cultures for polio vaccine production.<sup>3</sup> The Ebola hemorrhagic fever (EHF) is known to be the world's deadliest infection, and many people lost their lives this year due to this filoviral pathogen.

**Viral characteristics.** Ebola virus is a non-segmented, negative-sense, single-stranded RNA virus from the *Filoviridae* family. The genus of Ebola virus is classified into 5 different species (*Zaire*, *Sudan*, *Bundibugyo*, *Tai Forest*, and *Reston* agents) with differing virulence.<sup>4</sup> The *Zaire* subtype has caused multiple outbreaks with case numbers up to several hundreds since 1976. The

mortality reached 90% in these epidemics.<sup>5-8</sup> The Sudan virus has been associated with fatality in half of the cases in Sudan and Uganda outbreaks.<sup>9,10</sup> Interestingly, the Tai Forest virus has only been identified in one ethologist who performed a necropsy on a chimpanzee found dead in the Tai Forest. At the end, the patient survived.<sup>11</sup> The fourth species, Reston virus, differs markedly from the others, was identified only in an animal reservoir in the Philippines.<sup>12</sup> Finally, the Bundibugyo virus appeared in Uganda in 2007 causing an outbreak with 30% mortality.<sup>13</sup> In 2014, the first outbreaks occurred in remote villages in Central Africa, near tropical rainforests, but the most recent outbreak in west Africa involved the major urban as well as rural areas.<sup>14</sup> Molecular analysis indicated that the current virus was closely linked (97% identical) to variants of Ebola virus identified in the Democratic Republic of the Congo and Gabon.<sup>7</sup>

**Modes of transmission.** It is likely that Ebola virus is maintained in small animals serving as a source of infection for both humans and wild primates. Bats have long been at the top of the list of potential reservoirs since Marburg virus, filoviral hemorrhagic fever agent, was recovered from the fruit bats captured at a cave in Uganda.<sup>13</sup> Ebola virus has been known to be disseminating in nonhuman primates, seemingly as a result of their contact with unidentified reservoirs. This has contributed to a striking drop in chimpanzee and gorilla populations, and facilitated human outbreaks probably owing to the consumption of sick apes as food sources.<sup>15-17</sup> According to the Animal Mortality Monitoring Network found in Gabon and Congo, the carcass of duiker was tested positive along with primates in 2005.<sup>18</sup> Once introduced into the community, human to human transmission via contact with infected persons or their body fluids or secretions are considered the primary mode of transmission.<sup>19</sup>

**Impact of the current outbreak.** In March 2014, the Ministry of Health of Guinea reported a disease outbreak characterized by fever, severe diarrhea, vomiting, and a high case-fatality rate. The first cases occurred in Guéckédou and Macenta districts. In May 2014, the epidemic jumped to neighboring districts of Kenema and Kailahun in Sierra Leone, and in June it expanded to Lofa district in Liberia.<sup>19</sup> In September 2014, 5 countries from West Africa (Guinea, Liberia, Nigeria, Senegal, and Sierra Leone) documented EHF patients.<sup>20</sup> The disease had a deep impact in Guinea, Liberia, and Sierra Leone.<sup>19</sup> Moreover, the disease jumped to the United States of America (USA) and Spain with travel-

associated cases and localized transmission.<sup>21</sup> There have been 22,495 EHF cases, with 8,891 recorded deaths by February 1, 2015.<sup>22</sup> Thus, the average case fatality rate was approximately 40%.

According to the World Health Organization (WHO) Ebola Response Roadmap Situation Report, released on 26 October 2014, a total of 521 cases, including 272 deaths, had been reported among health care workers while caring for sick people.<sup>23</sup>

**Clinical presentation.** The pathogen is classified as a hemorrhagic fever virus based on its clinical manifestations comprising coagulation defects, a capillary leak syndrome, and shock. The Ebola virus has been known to be the most virulent human pathogen along with Marburg virus causing severe hemorrhagic fever, fulminant septic shock, and finally, death.<sup>24</sup> The course of infection, including signs and symptoms, incubation period (~11 days), and serial interval (~15 days), which is defined as the interval between disease onset in an index case patient and disease onset in a person infected by that index case patient were similar to that reported in previous outbreaks of EHF.<sup>19</sup> The most common symptoms were fever (87%), fatigue (76%), loss of appetite (65%), vomiting (68%), diarrhea (66%), headache (53%), and abdominal pain (44%).<sup>19</sup>

**Treatment and immunization.** Severely ill EHF patients require intensive supportive care, which is the mainstay of therapy.<sup>19</sup> In October 1, 2014, 2 candidates for EHF vaccines had clinical-grade vials available for phase-1 clinical trials. One of these formulations was cAd3-ZEBOV (GlaxoSmithKline, Raleigh, SC, USA) and recombinant vesicular stomatitis virus - Zaire ebolavirus (rVSV-ZEBOV) (Public Health Agency in Winnipeg, Canada). A series of coordinated phase-1 trials will be initiated in more than 10 sites in Africa, Europe, and North America.<sup>25</sup> Although no approved specific therapy is currently available in the treatment of EHF, several drugs such as brincidofovir, favipiravir, and ZMapp are under investigation for EHF. In the current outbreak, convalescent blood and plasma therapies have been used in a few patients. The numbers are too small to draw any conclusions on their efficacy.<sup>26</sup>

**Future prospects.** When an outbreak comes to an end, it is a matter of great concern. According to the WHO, an EHF outbreak in a country is reported to be over when 42 days have passed, and new cases have not been observed. The maximum incubation period for EHF was 21 days. The 42-day period was set by the WHO (twice the maximum incubation period) to provide a strong margin of security.<sup>27</sup> Currently, the

USA, Spain, Mali, Senagal, and Nigeria are categorized as affected countries.<sup>21</sup> Currently, EHF epidemic appears to be ending after the slowing of transmission.<sup>22</sup>

**Avian influenza A (H7N9) virus.** Influenza, usually known as “flu”, was defined by Hippocrates approximately 2,400 years ago.<sup>28</sup> The first considerable influenza-like illness pandemic recorded was of an outbreak in 1580, started in Russia and disseminated to Europe via Africa. During the outbreak, more than 8,000 people died in Rome.<sup>29,30</sup> The major historical flu pandemics and their deep impacts on mankind are presented in Table 1. In the last decade, H5N1 infections produced great anxiety with the advent of the new millennium, and remain the highest in occurrence with 60% lethality.

Three (H7N9, H6N1, and H10N8) avian influenza viruses broke the animal-human barrier in Asia in 2013.<sup>31</sup> One avian influenza case was detected in Taiwan due to H6N1 subtype, whereas 2 of 3 H10N8 human infections observed in China were lethal.<sup>31</sup> However, human infections due to H7N9 have been progressively increasing since its first identification in 2013, and approximately one-third of the H7N9-infected patients died.<sup>31-33</sup> Avian flu had the potential to spread “silently” among poultry and H7N9 infections did not cause severe disease in poultry, accordingly.<sup>34</sup>

**Viral characteristics.** Influenza is an infection of birds and mammals caused by RNA viruses from the family of *Orthomyxoviridae*. There are 2 main types of influenza virus, type A and type B. Type A viruses are the most virulent human pathogens among the other influenza types and cause the most severe disease. Influenza A viruses are divided into subtypes based on the hemagglutinin (H) and the neuraminidase (N) localized on the virus surface. So far, 18 hemagglutinin and 11 neuraminidase subtypes were documented.<sup>35</sup> Influenza B almost exclusively infects humans and is less common than influenza A.<sup>36</sup>

**Modes of transmission.** All identified influenza A subtypes other than H17N10 and H18N11 viruses have been found among birds and these 2 particular influenza subtypes were recorded in bats. Wild birds have been the primary reservoir for all influenza A viruses and have been believed to be the source of the diseases in all other animals.<sup>37</sup> In human influenza infections large amounts of influenza virus are often present in respiratory secretions of infected persons. Thus, the infection can be transmitted through sneezing and coughing, and is primarily acquired by large droplets (>5 microns).<sup>35,38</sup> This mode of transmission facilitated the dissemination of influenza in the history and resulted in major outbreaks. Further, animal flu viruses transmitted to humans are usually dead-end infections, and the virus does not have the capacity to be acquired between humans easily. This limitation is an important barrier to global dissemination. Accordingly, for human H7N9 infections, which are the focus of this review, the available information strongly indicated that they originated from infected poultry with either direct contact or indirect exposures such as visiting wet markets and contact with environments where infected poultry have been stored or slaughtered. Currently, there is no evidence of sustained, ongoing person-to-person spread of H7N9.<sup>39</sup> Since the influenza virus can be inactivated by soap, disinfectants, and detergents, frequent hand washing, and other sanitary measures reduce the risk of influenza transmission.<sup>40,41</sup>

**Impact of the current outbreak.** In late March 2013, novel human infections due to avian influenza A H7N9 virus were reported from China.<sup>32</sup> This particular influenza A virus had not previously been seen in either animals or people. The preliminary 133 cases were seen between February and May 2013. In this first wave, 44 patients died constituting a mortality of 33%, which was exceedingly high compared with other major historical pandemics.<sup>42</sup> Most of these patients were considered

**Table 1** - The major historical flu pandemics and impact on history.

Name of pandemic	Date	Deaths (million)	CFR %	Subtype
Russian flu <sup>54</sup>	1889-1990	1	0.15	Possibly H3N8 or H2N2
Spanish flu <sup>55</sup>	1918-1920	20-100	2.0	H1N1
Asian flu <sup>56</sup>	1957-1958	1-2	0.13	H2N2
Hong Kong flu <sup>57</sup>	1968-1969	1 to 4	<0.1	H3N2
Russian flu <sup>58</sup>	1977-1978	No accurate count	N/A	H1N1
Swine flu <sup>59,60</sup>	2009-2010	105,700 to 395,600	0.03	H1N1

CFR - case fatality rate, N/A - not applicable

to upsurge from exposure to infected poultry or contaminated environments. The number of new cases was highest in April 2013 and subsequently the patient flow dropped.<sup>43</sup> The probable reasons for this reduction were the implementation of control strategies, such as closing live bird markets, summer weather conditions, and increased public awareness. Studies indicated that avian flu viruses, like seasonal influenza, have a seasonal pattern and they circulate better in cold weather and less in warm weather.<sup>44</sup> Thus, a rise in the number of cases occurred in late 2013 and early 2014, coinciding with influenza season. More than 200 new cases have been confirmed during the second wave.<sup>45</sup> Until May 2013, H7N9 cases were reported from 9 Chinese provinces at the Pacific region. After this, H7N9 infections were reported from 12 provinces, indicating the rapid dissemination of the outbreak.<sup>46</sup>

In February 2014, the Malaysian Ministry of Health reported a human infection with avian influenza A (H7N9) in a traveler from China. This was the first imported case of H7N9 detected outside of China.<sup>47</sup> There have been other H7N9 cases detected until April 2014. In April 2014, Taipei Centers for Disease Control in Taiwan informed 2 laboratory reported patients, as the last reported cases as per the 27 June 2014 WHO report.<sup>48</sup>

**Clinical presentation.** The most common signs of influenza are fever, chills, sore throat, runny nose, severe headache, muscle pains, coughing, and fatigue.<sup>28</sup> Although it is often confused with other influenza-like illnesses, the common cold in particular, influenza is a more severe disease.<sup>49</sup> Complications of H7N9 virus infection include respiratory failure, acute respiratory distress syndrome, refractory hypoxemia, septic shock, acute renal dysfunction, multiple organ dysfunction, rhabdomyolysis, encephalopathy, bacterial and fungal infections like ventilator associated pneumonia, and blood stream infection with multidrug resistant bacteria.<sup>50</sup> Approximately, two-thirds of hospitalized patients are admitted to the intensive care units, indicating the severity of the illness.<sup>51</sup>

**Treatment and immunization.** The WHO Vaccine Composition Meeting for the 2014-2015 season held in February 2014 in Geneva approved that A/California/7/2009 (H1N1)pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, and B/Massachusetts/2/2012-like virus should be included in the trivalent vaccine formulation in the Northern Hemisphere.<sup>52</sup> Consequently, the aforementioned novel avian strains are out of scope of the current vaccine

formulation indicating the severity of the situation if the H7N9 influenza has global dissemination.

Laboratory testing in preliminary cases showed that neuraminidase inhibitors (oseltamivir, zanamivir) were effective against H7N9 infections, but the adamantanes were not. In addition, early treatment with neuraminidase inhibitors have been reported to restrict the severity of illness.<sup>34,53</sup>

**Future prospects.** Although it is likely that sporadic cases of H7N9 associated with poultry exposure will continue to occur in China, the virus has a pandemic potential, and it is possible that the virus can gain the ability to spread easily.<sup>49</sup> The future prospects of H7N9 infections are still unclear. However, there is no scientific evidence implying it will trigger a current global outbreak. Thus, international surveillance for H7N9 and other influenza viruses with pandemic potential is of paramount importance.

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