

## Editorial

# The Largest Ebola Outbreak— What Have We Learned So Far

DEBASHISH DAS,<sup>1</sup> PHILIPPE J GUERIN,<sup>2</sup> SANDRINE LEROY,<sup>3</sup> ABDULLAH ABU SAYEED,<sup>4</sup> M ABUL FAIZ<sup>5</sup>

The ongoing outbreak of Ebola virus infection in West Africa is the largest on record in terms of the unprecedented number of reported cases (n=18,603 at Dec 2014) and deaths (n=6915 at Dec 2014) and its' rapid transmission in dense urban populations. With an estimated mortality at around 70%, including massive death tolls in 365 health care workers (up to Dec 14, 2014), the epidemic has undermined fragile health-care systems and presented public health challenges that have never encountered before which is further constrained with the absence of treatment and vaccination options. Fast tracked testing of new or existing vaccines and drugs are currently being planned but are yet to be implemented in endemic countries. The development pipelines would offer a complementary approach to conventional outbreak control efforts. In an era of extreme global interconnectedness, a coordinated international response to improve public health capacity and clinical management in the worst affected countries needs to be scaled up urgently.

The global community is in the midst of the worst Ebola epidemic in history. The outbreak of 2014 Ebola virus disease (EVD) mainly affecting the West African countries of Guinea, Liberia, Sierra Leone, Mali (previously affected Nigeria, Senegal) has claimed a death toll of 6915 with 18,603 identified cases (confirmed, probable, suspected), as of December 17<sup>th</sup>, 2014.<sup>1</sup> In early August, 2014, the World Health Organization (WHO) declared the West African Ebola outbreak a "public health emergency of international concern (PHEIC)." The outbreak has also been declared a threat to international peace and security by the UN Security Council. The rapid spread of EVD yielding a deadly toll on health care professionals, 365 deaths out of 649 cases as of 14<sup>th</sup>

December, 2014<sup>1</sup> with its emergence in the capital cities makes the outbreak response challenging and fuels widespread concern.

Ebola virus was identified in 1976 in Yambuku, the Democratic Republic of Congo (then Zaire) and Nzara, southern Sudan, and named after the Ebola river in Zaire.<sup>2</sup> Ebola virus and Marburg virus constitute the family Filoviridae in the order of Mononegavirales. Filoviruses are enveloped, non-segmented, negative stranded RNA viruses, with characteristic filamentous particles. Ebolaviruses comprise five separate species – *Zaire*, *Sudan*, *Tai Forest*, *Bundibugyo*, and *Reston virus*. The virulence of human Ebola virus varies according to its species. The Zaire virus infection is the deadliest of the known Ebola species with the highest case-fatality rates (60-90%), the Sudan virus species with 40-60% and in a single outbreak, the Bundibugyo virus with estimated rates of 25%.<sup>3</sup> There has been only a single reported nonfatal case by the Tai Forest virus. Reston virus has not been associated with human disease and is found in the Philippines.

The early symptoms of EVD resemble symptoms of many common diseases, including malaria, as well as Lassa haemorrhagic fever, yellow fever endemic in West Africa. Humans infected by Ebola virus commonly present with fever, vomiting, diarrhoea, headache, joint and muscle aches, abdominal pain and haemorrhage, with immunosuppression, increased vascular permeability, and impaired coagulation leading to multiorgan failure and shock.<sup>3,4</sup> The abrupt onset of EVD follows an incubation period of 2-21 days and transmission occurs through body fluids: faeces, vomit, blood, semen and sweat. The patients become infectious when they are symptomatic, and corpses remain highly contagious. Controlling transmission requires minimising contact with bodies, body fluids, and contaminated items. It has been described and therefore considered very unlikely that transmission occurs through breathing or insect bites.

Ebola virus infection is a zoonosis with persistence of the virus in a reservoir species.<sup>5</sup> Great apes, man, and other mammalian species susceptible to Ebola virus infection are considered as end hosts and fruit bats are thought to be potential reservoir species. Bats are frequently encountered in equatorial Africa and hunted for food in many places. Ebola virus might persist as an asymptomatic or subclinical

1. Service du BESPIM, Unit EA2415, Université de Montpellier 1, France
2. Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK
3. Department of Biostatistics, Caremeau Hospital, Nimes, and EA2415 Unit, Montpellier University, Montpellier, France
4. Chittagong Medical College, Chittagong, Bangladesh
5. Dev Care Foundation, Dhaka, Bangladesh. Former Director General of Health Services, Government of the People's Republic of Bangladesh

**Correspondence :** Prof. Dr. M Abul Faiz, Dev Care Foundation, Dhaka, Bangladesh. Former Director General of Health Services, Government of the People's Republic of Bangladesh. E-mail: drmafaiz@gmail.com

infection in the reservoir species, with little or no transmission. Introduction into human most likely occurs through direct contact with bats, their excretions or secretions, or through the ‘bushmeat’ (considered as a delicacy) of primates, forest antelope, wild pigs, and bats. Transmission through droplets, contaminated food and water, and through asymptomatic individuals has not yet been documented and is unlikely. The discovery of Reston Ebola virus in pigs in the Philippines raises the possibility of having other reservoir species or potential amplifying hosts.<sup>6</sup>

Previous EVD outbreaks were confined to remote regions of Central Africa, whereas the current 2014 outbreak started in Guinea, West Africa and spread into major cities Conakry (Guinea), Monrovia (Liberia), Freetown (Sierra Leone) and Lagos (Nigeria)<sup>7</sup> and still expanding exponentially with an estimated mortality at around 70%. In a recent genomic surveillance, scientists have elucidated Ebola virus’s origin, transmission dynamics and evolution during the 2014 outbreak through viral sequencing and observed a rapid accumulation of interhost and intrahost genetic variation. The study concluded that the West African variant most likely diverged from Central African lineages 2004, crossed from Guinea to Sierra Leone, and has exhibited sustained human-to-human transmission subsequently, without any evidence of additional zoonotic sources.<sup>8</sup>

To date, in the absence of an approved therapy or vaccine, treatment is mainly palliative and prevention of transmission is limited to barrier methods. Aggressive supportive care initiated as early as possible with maintenance of fluids and electrolyte balance and hemodynamic monitoring is crucial. The limited number of patients have had accessed to state of the art intensive care have a better survival rate than patients currently treated in resource- constrained environments.

In practice, conducting clinical trials or introducing experimental techniques in a complex emergency setting are quite challenging. Furthermore, the market for Ebola drugs and vaccines looks unpromising and before the current epidemic, most research has been conducted in response to worries about biowarfare and bioterrorism. Facing the current public health emergency, and the limited prospect that “classical” isolation measures will provide an adequate response, Ebola vaccines and drugs are now an urgent international priority. There were intensified debates among scientists, government officials, and pharmaceutical executives about bringing unapproved products to Africa on a compassionate use basis, and on the optimal designs to test and register new products.<sup>9</sup> Currently, Ebola vaccines and drugs are considered for field testing. Recombinant

vesicular stomatitis virus (VSV)-based vaccine from Newlink Genetics and the Public Health Agency of Canada and NIAID/GSK cAd3 Ebola vaccine are leading vaccine candidates.<sup>10</sup> Both vaccine candidates have shown 100% efficacy in studies in nonhuman primates.<sup>11</sup> Several other vaccine candidates are at earlier, preclinical stages in the development pipeline. Fast-tracked Ebola trials for evaluating the promising investigational drugs have been planned in affected countries in West Africa recently as part of an international initiative.<sup>12</sup> Favipiravir, an influenza drug which is approved for treatment of pandemic influenza in Japan, is currently being considered for clinical testing. Other candidate drugs, such as amiodarone, toremifene, interferon, are already approved for treating non-Ebola diseases but yet to be proven their utility in EVD. Among the rest of the therapies in development pipelines, the potential candidates include Zmapp, TKM-Ebola (RNAi-based), a polymorpholino oligonucleotide PMO-RNA, and Brincidofovir (Personal communication).

In addition to individual therapeutic approaches, Ebola control relies on decreasing transmission occurring at hospitals, funerals and at community level. Ending previous Ebola outbreaks typically relied on stopping transmission in hospitals through strict infection control measures, adapting safe burial practices to reduce risk of transmission, and active case-finding (tracing contacts of known cases and then monitoring and isolating suspected cases). In order to mitigate the risks for health care workers and to prevent spread of EVD, trained workforce, isolation units, personal protective equipment (PPE), and barrier nursing techniques are essential in health care settings. It must be a stress that health care workers are at high risk of contracting the disease estimated at >100-times the one of the general population in the recent outbreak. The use of common PPE is challenging in tropical context as heat and discomfort limit time health personnel can wear them. Passive case-finding with community isolation (i.e., people can voluntarily come to be isolated if they suspect that they have the disease) could be an important strategy to reduce community transmission.<sup>13</sup> Reducing transmission from the dead is rather complex and infection control protocols need to be adapted to local burial practices. In West Africa, family members and funeral-goers often have extensive contact with the dead body as burial rituals. Protocols for handling and disposing of a body to minimize the risk of infection must be implemented through dialogues with Ebola-stricken communities with their engagement, cooperation and consent.

In this ongoing public health crisis, accurate and timely information dissemination, open data are crucial to implement

an effective response effort. However, dissemination of data and coordination haven't yet been optimal. Robust data-capture systems are needed to be implemented in the worst-affected countries to understand transmission dynamics but this is proven to be challenging in countries with overwhelming health services. Mathematical models can be useful tools for transforming data into useable knowledge and can help to predict different provisions in epidemic response mechanism. The force of transmission of a disease outbreak is quantified as R (the reproduction number) – the number of people infected by one sick person, on average, in an outbreak, when everyone in the population is susceptible to the disease. The reproduction number tells how contagious an infectious disease is. When R=1, the transmission is stable and a disease is considered endemic. Getting R below 1 is a strategic priority of the response effort at this stage of the outbreak. Many factors contribute to the R, such as how long a person is infectious and how many virus particles are needed to make another person sick. Reducing R depends on various factors, including reducing the risk of transmission by decreasing time between when people first show symptoms and are being isolated. Based on available limited epidemiological data, overall basic reproduction number (R0) for the ongoing epidemic has been estimated to be 42.0<sup>14,15</sup> and model predicts that isolating ~70% of Ebola cases within three days of their becoming symptomatic is key to pushing R to less than 1.<sup>13</sup> Thus early detection of population at risk is crucial to stop the outbreak.

The threat of the spread of Ebola infection in Asia and in Bangladesh in particular isn't high, even though, preventive measures have been promptly taken. Amongst them, the introduction of screening processes at all international airports and sea ports of travellers entering the country from Ebola affected regions, attempts to identify possible suspected cases on arrival. Further, isolation units for any such possible cases and measures to ensure provision of PPE for the health professionals have all been introduced. Despite such steps the deployment of several hundred Bangladeshi peace keeping troops currently in the afflicted West Africa region remains a concern. Thus already considered protective measures for the peacekeepers need to be scaled up and coordinated urgently.

Constant human movement between affected countries and beyond, pose serious threats to epidemic containment efforts. Experts also fear about the migrant workers from densely populated Bangladesh or India who work in trade or industry in West Africa.<sup>16</sup> For instance, a migrant worker becomes infected by Ebola virus, and travels back home to see family and friends during the virus's incubation period,

and afterwards, visits a public hospital there. Health care providers, such as doctors, nurses, paramedics in Bangladesh-India often don't wear protective gloves and might not be aware of the risk. In the unlikely event of an importation of an Ebola case in Asia, promptness and coordinated response will be the key for the success of containment as was demonstrated in Nigeria. Moreover, a bat associated paramyxovirus infection, Nipah virus infection, has been found to cause an almost yearly limited outbreak of encephalitis in the Bangladeshi population amongst those who consume raw date palm sap. The Nipah virus has the potential for human-to-human transmission.<sup>17</sup> Nipah virus infection causing high mortality and residual neurosequale, remains a unique emerging zoonotic infection yet to be contained and effectively addressed in the region. As fruit bats are one of the leading suspects of Ebola virus carrier, the wildlife epidemiologists need to see if the bat species in the Indo-Bangladesh region have the potential to harbor the virus.

Ebola virus, one of the most virulent infectious agents known to human, has generated worldwide impact through imported infections and exposed the limitations of resource limited public health systems to respond promptly to highly virulent communicable diseases.<sup>18</sup> Despite years of research on Ebolaviruses, the world community finds itself today in very much in the same place as it did during the first reported outbreak in 1976. In the upcoming months, vaccines and drugs will be tested but yet the international community will have to make them available in substantial quantity to respond to this exceptional Ebola virus outbreak. Even if an effective vaccine and drug can be produced, there is an extraordinary need for a coordinated response effort to improve capacity and provide clinical care in affected countries. From global perspective, we need to fill the remaining gaps in epidemic containment efforts before Ebola or a related virus strikes again in near future.

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