Brief Communication

The Deadly Ebola Threat in the Midst of an Overwhelming Dengue Epidemic

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Submitted: 24 Oct 2014
Accepted: 26 Oct 2014

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Abstract

The recent death tolls and morbidities associated with two deadly viral haemorrhagic fevers (VHFs), i.e., Ebola and dengue, are simply shocking. By the end of August 2014, 65 672 people were afflicted with dengue fever (DF) in Malaysia, with 9505 from Kelantan, and there were 128 reported deaths. More astounding are the death tolls associated with Ebola: 3091 deaths from 6574 reported cases so far. It is not difficult to imagine the potential disaster if Ebola spreads beyond Africa. VHFs are characterised by an acute onset of fever, vascular disruption and a rapid progression to shock and death. The revised World Health Organization (WHO) 2012 classification (dengue with and without warning signs and severe dengue) is more clinically relevant and allows more streamlined admission. With good administrative support and public health and governmental efforts, the dengue epidemic in Malaysia is now more contained. However, there should be no laxity with the imminent lethal Ebola threat. Human-to-human transmission is an important mechanism for the spread of Ebola, and this calls for strict precautions regarding contact with any suspected cases. In contrast, the control and elimination of dengue would require successful control of the vectors and their breeding sites.

Keywords: *Ebola, dengue, hemorrhage, fever, virus*

The Shocking Numbers

The world has been shaken by the recent unprecedented morbidity and mortality caused by two viral haemorrhagic fevers (VHFs), i.e., Ebola and dengue. The initial triggering of the Ebola outbreak in West Africa in the beginning of 2014 closely followed the dengue epidemic in Asia. At one extreme, Ebola viral disease (EVD) has a fatality rate above 90% (1), whereas dengue fever (DF), at the other end, is associated with significant morbidity. The dengue epidemic in Malaysia this year, especially in the state of Kelantan in the northeastern region of the Peninsular, has been the worst ever, stretching the limits of the national health care system. DF causes significant economic loss because this disease affects mainly healthy young people. By the end of August, a total of 65 672 people were confirmed to have DF in Malaysia, with 9505 people from Kelantan. So far, there are 128 reported deaths, based on national figures, and these numbers have far exceeded any previous records (2,3). More astounding, however, are the death tolls associated with the Ebola outbreak; by the end of September of this year, there were 3091 deaths from 6574 reported cases (4). On September 30th, the first travel-associated case of Ebola was announced outside of West Africa (4), indicating a real danger that this disease may spread to the rest of the world.

Deadly Viral Haemorrhagic Fevers (VHFs)

Collectively, VHFs affect more than 100 million people around the world and kill more than 60 000 annually (5). The diseases brought about by viruses in the VHF group are characterised by an acute onset of fever and vascular dysfunction, with a potential for bleeding disorders (5,6). These diseases can rapidly progress to shock and subsequently death. The 23 enveloped RNA viruses associated with VHFs are grouped into four taxonomic families, i.e.,

Arenaviridae, Bunyaviridae, Filoviridae, and *Flaviviridae* (6). These viruses share a number of common features. First, they are enveloped viruses with single-stranded ribonucleic acid (ssRNA) genomes and cytoplasmic replication (5). Second, they use rodents, bats, or insects as natural reservoirs or vectors (5). As a result, their distribution is geographically limited by the habitats of their natural hosts, and human beings are incidental hosts. Most of these viruses show affinity to most bodily cells (pantropism), but they preferentially target dendritic cells (DCs), monocytes and/or macrophages (5). The mechanisms of vascular dysfunction in VHFs include endothelial damage, activation of mononuclear phagocytes, expression of abnormal levels of cytokines and other mediators, platelet aggregation and consumption, initiation of the coagulation cascade, and insufficiency of coagulation factors because of severe hepatic damage (6). Thrombocytopenia and depressed immune responses are the hallmarks of VHFs (5). A body of evidence that indicates the importance of viral replication and host immune responses in determining the disease severity and clinical outcomes is available (5).

Overwhelming Dengue Epidemic in Malaysia

Dengue virus (DENV), from the *Flaviviridae* group of viruses, is the most prevalent cause of arthropod-borne VHFs (5). A third of the world's human population is at risk for exposure to dengue (7). Annually, there are approximately 50 million reported cases of DF, with 500 000 of them requiring hospitalisation, and there are between 20 000 and 25 000 reported deaths (7,8). The primary vector for DENV is the mosquito *Aedes aegypti*, which has been urban adapted, and the secondary known vector is *Aedes albopictus,* which has expanded its geographical distribution in more recent years (7). Any of the four single-stranded, positive-sense RNA virus serotypes (DENV serotypes 1 to 4) can cause DF (7,8). DF is one of the most common causes of acute febrile illness among children in the Asia-Pacific region (9) and is among the leading causes of hospitalisation (10). Although dengue is not as fatal as the other types of VHFs (namely, yellow fever or EVD), the mortality rates of complicated dengue, i.e., dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), have been reported to be between 1% and 5% at high-volume centres (10). However, the mortality rates can reach 44% in the presence of established shock (10).

One of the major challenges is to identify the patients who might develop the severe form of dengue. Among the risk factors for severe dengue reported in the recent literature are female gender, young age, obesity, the virus strain, genetic variations, and the presence of secondary dengue infection (two sequential infections by different serotypes) (8). Recognising the clinical limitations of earlier classification (classical dengue fever, DHF and DSS), in 2012, the WHO revised the classification to include dengue without warning signs, dengue with warning signs and severe dengue (11). This newer classification is meant to simplify the patients' categorisation, to make the criteria more clinically relevant, and to make it easier to monitor progress at the bedside. Furthermore, based on this classification, admission is more streamlined, i.e., those without warning signs can be managed at home with home monitoring, those with warning signs should be admitted to a general ward and those meeting the criteria for severe dengue should be admitted to a high-dependency unit (HDU) or intensive care unit (ICU).

During the dengue outbreak, Hospital Universiti Sains Malaysia, one of two tertiary hospitals serving the state of Kelantan, admitted a total of 1252 patients with DF from January 1st to September 30th of this year. The majority of patients were admitted to the general ward, 166 (13.3%) of whom had severe dengue. For the first three quarters of this year, there were 4 (0.3%) dengue-related deaths (Figure 1). With the alarming growing figures, the hospital administration, in cooperation with the Ministry of Health of Malaysia, was quick to take action. In addition to creating two new general wards dedicated solely to the outbreak, the whole 6-bed surgical ICU was readied for any cases of severe dengue. The wards and ICU were supported by a dedicated team of doctors, nurses and attendants who were on duty 24 hours per day, 7 days per week, for months.

The Imminent Worldwide Threat of Ebola

The onslaught of dengue has barely settled, and a potentially imminent wave of Ebola is threatening to hit the Malaysian shore. On August 8th, 2014, the WHO declared the Ebola epidemic to be a public health emergency of major international concern (12). This declaration was made after the realisation that an international spread of Ebola could have serious implications

(12). This concern is not exaggerated and should not be ignored by any governments, including the Malaysian government. There is unpredictable and continuing disease transmission and high case fatality rates for Ebola in West African countries (Guinea, Liberia, Sierra Leone, and Nigeria), and the weak health services in these and other neighbouring countries would not be able to contain the epidemic without any international support (12). The current outbreak of Ebola has much similarity to the 1976 outbreak. Both were caused by *Zaire ebolavirus* and began in rural forest communities where wild animals were hunted for food. Acutely ill patients started to come to district hospitals in large numbers, with initial symptoms resembling more common

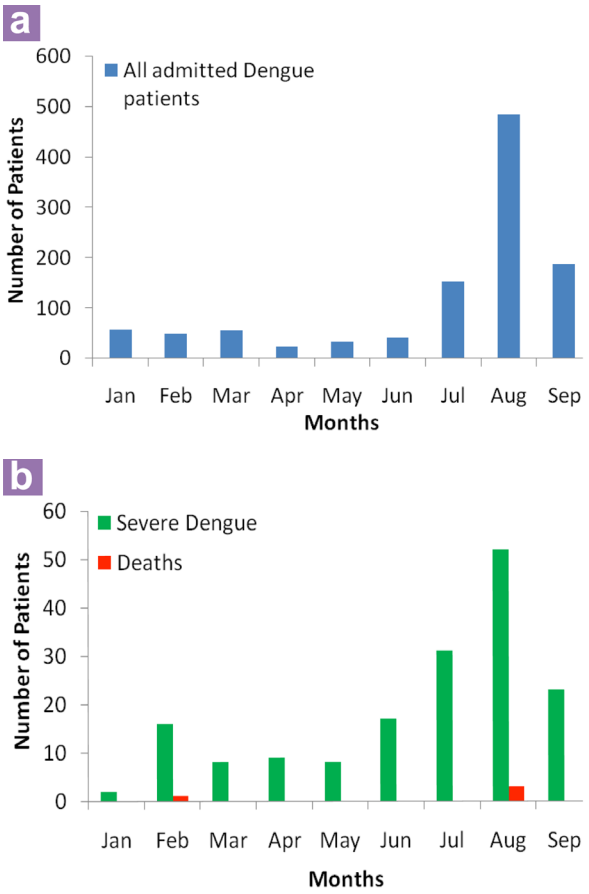

Figure 1: Patients admitted into Hospital Universiti Sains Malaysia from January to September 2014: (a) total number of admitted patients with confirmed dengue and (b) number of patients with severe dengue (green bar) including number of deaths (red bar).

infections, including malaria, typhoid, Lassa fever, yellow fever, and influenza. In addition to unknowing relatives, families and friends, unprepared hospital staff members who were in contact with the patients' blood and bodily fluids then became ill themselves. The disease quickly spread to the cities, and chains of transmission were then established (13).

A member of the Filovirus family, Ebola viruses are pleomorphic, negative-sense RNA viruses with genomic organisation similar to that of the Paramyxoviridae. Of the four identified strains, three, or the Zaire, Ivory Coast, and Sudan strains, have resulted in diseases in both humans and nonhuman primates, with the Zaire strain being the most lethal (14). This virus replicates at abnormally high rates that overwhelm the protein synthesis engine of infected cells and easily defeat the host immune defences (14). Direct infection of monocytes and macrophages and the resultant host immune responses cause the release of cytokines commonly associated with inflammation and fever. Additionally, the direct cytopathic effect on the endothelial linings, together with abnormal cytokine effects, results in loss of the vascular barrier, haemorrhage and subsequent total vasomotor collapse (14). These effects on the vessels are the causes of the high mortality rates observed for Ebola.

Ebola vs Dengue: The Conclusion

Although EVD shares a number of similarities with other VHFs, there are differences that set them apart (Table 1). One of the important differences between EVD and dengue is the mode of transmission. Whereas there is human-to-human transmission via contact with blood or bodily fluids for EVD, there is no human-to-human transmission of dengue. Therefore, a major intervention to control the spread and dissemination of EVD would be strict observation of precautions regarding contacts when handling patients under investigation or any confirmed cases of EVD. In contrast, the control and elimination of dengue would require successful control of the vectors and their breeding sites.

Acknowledgement

None.

Funds

None.

Table 1: Comparison between dengue hemorrhagic fever and Ebola viral disease

	Dengue hemorrhagic fever	Ebola viral disease
Family	Flaviviridae	Filoviridae
Mode of transmission	Anthropod-born	Direct Contact with Blood/Body fluid
Human-human transmission	No	Yes
Incubation period	3 to 7 days	2 to 21 days
Mortality	0.04 to 0.05 %	50 to 90 %
Typical Symptoms:		
Fever	Common	Common[15]
Headache	Common	Common[15]
Muscles ache and pain	Common	Common[15]
Vomiting	Common	Common[15]
Diarrhea	Uncommon	Common[15]
Bleeding	Unusual	Usual[15]
Typical blood Abnormalities:		
Platelet	Low	Low[16]
White cells counts	Low	Low[16]
Hematocrit	High	Low[16]
Hemoglobin	High	Low[16]
Aspartate transferase	Elevated	Elevated[16]
Treatment	Supportive	Supportive

Conflict of Interest

None.

Authors' Contribution

Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for the important intellectual content, final approval of the article, provision of study materials or patient, statistical expertise, obtaining of funding, administrative, technical or logistic support, collection and assembly of data: AMB, SSMN, YYL

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