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MINI REVIEW

Zika virus: A possible emerging threat for Bangladesh!

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ABSTRACT

Zika virus, a member of *Flaviviridae* is the etiology of Zika or Zika fever or Zika virus (ZIKV) disease characterized by mild symptoms similar to very mild form of Dengue or Chikungunya. The virus transmits through *Aedes* mosquitoes, particularly by *Aedes aegypti*. The most dangerous effect of ZIKV infection is the ability of the virus to cause microcephaly and congenital malformation to the newborn baby if the mother is infected. The neurological disorders including Guillain-Barré syndrome might be associated with adults and children due to ZIKV infections. Zika has emerged as a serious global public health problem as it has been found in 87 countries, particularly in Africa, America, and Asia and has no vaccine and treatment so far. Bangladesh is at a high risk of ZIKV infection and we consider ZIKV as a possible emerging threat for Bangladesh. This short review summarizes the insights of ZIKV infection, present status of the disease in Bangladesh and its neighboring countries, and recommendations for necessary preparations and strategies to be taken for effective controlling of the ZIKV infection in Bangladesh before getting any havoc.

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Introduction

Zika virus (ZIKV) infection is one of the important infectious diseases of human caused by ZIKV belonging to the genus *Flavivirus* under the family *Flaviviridae*, which includes 52 other viral species including dengue and chikungunya viruses [1,2]. It is synonymous to Zika fever or Zika or Zika virus disease. Most of the ZIKV infections are asymptomatic and, if symptoms appear, are similar to Dengue and Chikungunya [3]. However, ZIKV might be fatal for the fetus and many neurological disorders may occur in infant and adults as well [4–6]. So far, there is no preventive vaccines and medicines against ZIKV infection [7].

Like other flaviviruses, ZIKV is an enveloped virus containing a single stranded 10-kb positive sense RNA genome with icosahedral capsid [8,9]. During biting, ZIKV present in the saliva of mosquitoes infects the epidermal keratinocytes, skin fibroblast, and Langerhans cells. Then, the virus spreads to lymph lodes and blood stream. The RNA genome is directly translated into a long polyprotein within the cell cytoplasm which further cleaved and processed by viral or host proteases into three structural and seven nonstructural proteins. The nonstructural proteins play important roles in viral genome replication and manipulating host responses, whereas structural proteins involve in viral particle formation [9,10].

Though the virus was first isolated from a rhesus macaque monkey (*Macaca mulatta*) in 1947 from the Zika forest of Uganda, it has been confirmed in 1952 by a serological survey in the same country that ZIKV can infect human [11,12]. However, now a day, ZIKV infections have been reported around the world including Asian countries (Fig. 1) [13–18]. The epidemiological data from different countries are limited, but new information regarding ZIKV transmission patterns, incidence, and prevalence has been gathering time to time by recent studies [19]. The first major outbreak of ZIKV infection was reported at Micronesia in 2007 where about 75% of the people

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have been affected followed by a second large outbreak in French during 2013–2014 [20]. Severe outbreak of ZIKV infection occurred in Brazil in 2015 with increase cases of microcephaly [21].

The ZIKV cases have been sporadically reported in many countries in the world [19,22]. World Health Organization (WHO) reported that 87 countries of the world had evidence of ZIKV infection until July 2019 [19]. Because of such increasing incidence of ZIKV infection throughout the world, severe pathological manifestations and lack of vaccine and treatment, Zika became a serious public health emergency of international concern [23]. Presence of ZIKV infection in Bangladesh has been reported in 2013 and 2014 by the detection of immunoglobulin G (IgG) and polymerase chain reaction (PCR) confirmation from serum sample [24,25]. However, there is no evidence of the current outbreak of ZIKV in Bangladesh that might be due to very limited information regarding surveillance, detection, and reporting systems for new cases. According to recent reports, Bangladesh is endemic for Dengue which is also transmitted by *Aedes* mosquitoes as well [26,27]. ZIKV might follow the path of spreading Dengue and Chikungunya throughout the world [28,29]. Therefore, it is crucial to investigate Zika throughout the country with proper diagnosis so that effective prevention and control measures can be adopted before an endemic occurs. In this short review, we have discussed the Zika outbreaks in the context of Bangladesh and neighboring countries and future perspective of ZIKV surveillance, diagnosis, prevention measures, and research need to be taken in Bangladesh.

Zika Virus Transmission and Pathogenesis

ZIKV primarily transmits and spreads by the biting of infected female *Aedes* mosquito, primarily by *A. aegypti and Aedes albopictus.* The virus can also be transmitted by other species of mosquitoes such as *Anopheles*, *Culex*, *Eretmapodites*, and *Mansonia* [30]. This virus can also be transmitted by sexual intercourse, blood transfusion, saliva, urine, and from infected pregnant women to her babies (Fig. 2) [5,31–35]. Though ZIKV infections might be asymptomatic, the infected patients may have fever, red eyes, joint pain, headache, conjunctivitis, retro-orbital pain, fatigue, and maculopapular rashes which are similar to that of Dengue and Chikungunya, but may cure within a week [3]. However, it may cause severe diseases such as multi-organs failure, thrombocytopenia

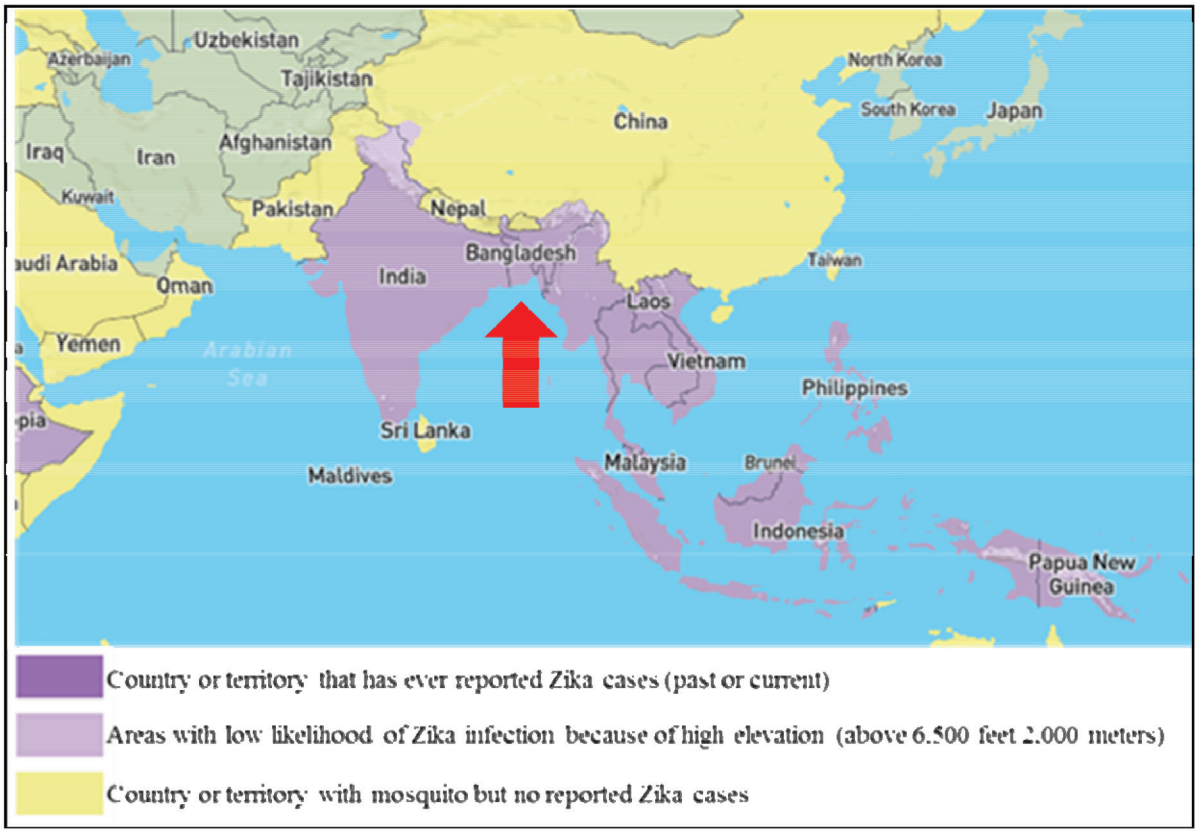

Figure 1. Outbreak (Risk) of Zika infection in different Asian countries (https://wwwnc.cdc.gov/travel/page/zika-travel-information). Red arrow indicates the location of Bangladesh (23.6850°N, 90.3563°E).

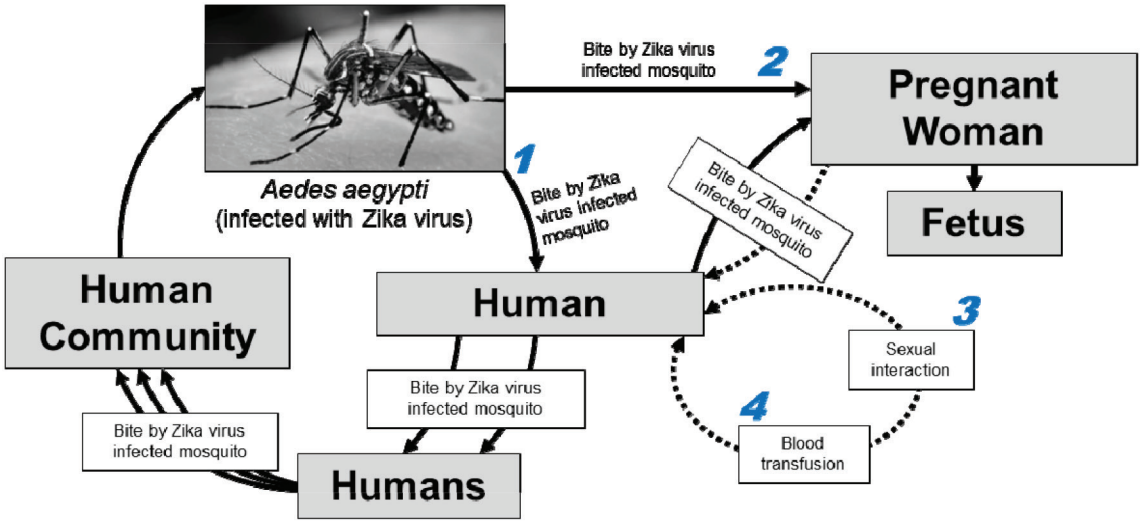

Figure 2. Transmission of Zika virus. (1) Infected mosquito (particularly female *A. aegypti*) may bite a healthy human. The Zika infected human may act as a source of infection for other humans in the community. (2) Infected pregnant woman may act as a source for Zika virus transmission to her fetus. (3) Human to human transmission may occur by sexual interaction between male and female. (4) Blood transfusion may cause Zika virus transmission from one human to another.

and thrombocytopenic purpura, meningitis, encephalitis, and Guillain-Barre syndrome [36,37]. Miscarriage and stillbirth may found if the ZIKV infection happens during pregnancy [5,38,39]. The most dangerous effects are microcephaly, neurodevelopmental injuries of fetus, and the congenitally infected baby may show hypoplasia of the cerebellum and brainstem, ventriculomegaly, delayed myelination, enlarged cisterna magna, abnormalities of the corpus callosum, calcifications, and cortical malformations [40,41]. However, ZIKV infected patient may also show local hyperemia and petechiae on the hard palate [42,43].

Zoonosis

Monkey and apes could be infected with ZIKV with mild signs of illness. Few monkeys were diagnosed positive with ZIKV in Brazil with high number of human cases [44,45]. One study in Indonesia at 1970s reported that horse, cows, water buffaloes, goat, duck, and bat could be infected with ZIKV without clinical symptoms and having no evidence of transmission to human [46]. Though no microcephaly has been reported in the Zika endemic areas, further research is needed for better learning the ZIKV and microcephaly in animal pregnancy as suggested by the Centers for Disease Control and Prevention (CDC) and others scientists [47].

Diagnosis

Clinical symptoms of ZIKV infections are very similar with Dengue and Chikungunya with few distinguished features [48]. In ZIKV, there is low grade fever, while fever is high in Dengue and Chikungunya infection. On the other hand, edema of limb is very common in ZIKV, which is absent in Dengue and Chikungunya. In addition, unlike Dengue and Chikungunya, arthralgia is very less common in ZIKV. The asymptomatic pregnant women should be tested according to CDC guideline [49]. Confirmatory diagnosis of ZIKV is based on reverse transcription PCR (RT-PCR) and enzyme-linked immunosorbent assay (ELISA), and laboratory tests are useful to distinguish Zika from other flaviviruses. ELISA and immunofluorescence assay of serum samples 5–7 days onward of clinical symptoms appeared are useful to detect ZIKV specific IgM. It is recommended to test the serum samples again for the second time from 1 to 2 weeks after the first sampling as ZIKV-specific IgM may persist up to 12 weeks of post symptoms. In special circumstances such as with specific history or disorder, cerebral spinal fluid, urine, saliva, amniotic fluid, nasopharyngeal swabs, placenta, umbilical cord of infant, etc., can be used for diagnostic purpose [50–52]. Nucleic acid amplification test (NAAT) can be used to detect the viral RNA. ZIKV RNA can be detected in serum up to day-10 after the symptoms appeared [53]. Urine samples would be the alternative way for NAAT [34]. However, ZIKV diagnosis from the serum samples of a patient having history of other flaviviruses can cross-react in the tests. WHO recommended an algorithm for differential diagnosis of ZIKV with Dengue and Chikungunya (Fig. 3). Recently, several rapid diagnostic kits such as Zika NS1 Rapid Test (Biopanda Reagents, The United Kingdom), Zika Rapid Test (Maternova, USA), and Artron's One Step Zika Virus Test Kit (Bio-Connect Diagnostics, The Netherlands) specific for ZIKV have been

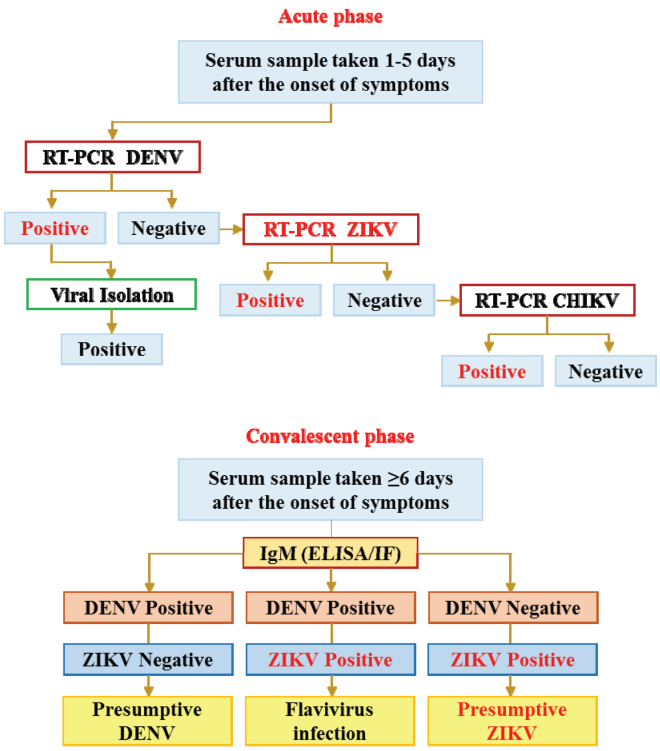

Figure 3. Algorithm for detecting ZIKV from the suspected case of infection due to arbovirus. The algorithm is re-prepared from ZIKV Surveillance in the Americas: Laboratory detection and diagnosis by WHO/PAHO (Pan American Health Organization; https://www.paho.org/hq/dmdocuments/2016/2015-cha-algorithm-detecting-zikv.pdf).

developed which can be used for primary detection in the field level [54].

Prevention

Currently, there is no vaccine against ZIKV in the market; however, some vaccines are under the developmental stage including a trial in animal model [55–57]. As ZIKV is primarily transmitted through *Aedes* mosquitoes bite, mosquitoes control can be the prime strategies to control the ZIKV infection [58]. The standard *Aedes* mosquitoes' control strategies have been mentioned by CDC and WHO [48]. The pregnant women have been suggested to avoid unnecessary travel to the areas of ongoing ZIKV transmission. The unprotected sexual contact with the person having the risk of ZIKV infection should be avoided.

Zika Virus Infection in Neighbor Countries of Bangladesh

Although the origin of ZIKV is in Uganda, currently it has been reported from 87 countries of the world including Asia (Fig. 1) [19]. According to WHO, till December 2018, around 159 cases of ZIKV infections have been identified in India, the neighboring country of Bangladesh [19]. All these cases were detected based on RT-PCR, of which 63 were found in pregnant women. The infection was reported at four regions of India, i.e., Tamil Nadu, Rajasthan, Gujarat, and Shastri Nagar area of Jaipur [59]. A strong monitoring team of expertise at National Centre for Disease Control (NCDC) was formed in India to monitor preparedness and response measure for ZIKV infections [60]. A recent study conducted on 462 samples collected from patients showing Dengue symptoms and asymptomatic patients during the year from 2004 to 2017 in Myanmar; however, ZIKV infection has been confirmed in 4.9% of patients showing the Dengue symptoms and 8.6% in asymptomatic persons at Mandalay and Yangon, respectively [61]. The most recent assessment showed long term and wide spread ZIKV infection is circulating since 2006 in Thailand [62]. A total of 3,089 samples were analyzed from 1,717 symptomatic patients from January 2016 to December 2017 among 76 Thai provinces, and 368 cases were confirmed as ZIKV infection at 29 provinces which were reported [62]. ZIKV clinical surveillance and Flavivirus laboratory performed a comprehensive and systematic study in Malaysia by collecting suspected flavivirus samples between June 2015 and December 2017. Though only 8 out of 4,043 suspected samples were positive for ZIKV but two pregnant women confirmed with the infection [63]. There is evidence of ZIKV infections in Nepal and co-infection with Dengue virus in Singapore as well [64–66]. Most importantly, 10 Bangladeshi people living in Singapore were affected by ZIKV as reported by Singapore Ministry of Health at August 2016 [67].

Risk Analysis of Zika in Bangladesh

The ZIKV infections was first reported in Bangladesh at 2013 by a seroprevalence study and ZIKV neutralizing antibodies were detected onward from 2013 [25]. In 2014, another ZIKV infection was reported in Chittagong district of Bangladesh, and has been confirmed by RT-PCR in serum samples followed by partial *E* gene sequencing and phylogenetic tree analysis [24]. The only clinical signs of the patient were fever for 5 days and maculopapular rash on body having no overseas travel history within last 2 weeks of symptoms appeared. However, this Bangladeshi ZIKV was closely related with Brazilian and South American strains [24]. As far we know, until that there is no other report of ZIKV infectious in Bangladesh, Does it mean really there is no ZIKV infection in Bangladesh? ZIKV has been circulating among almost all the neighboring countries of Bangladesh, namely, India, Myanmar, Malaysia, Nepal, and Singapore [19,59–66]. Bangladeshi people living in Singapore have been also affected by ZIKV [67]. Peoples are also frequently visiting these neighboring countries, enabling easy entry of the ZIKV to Bangladesh. Moreover, many Burmese (Rohingya) recently entered

Bangladesh could also be the potential source for ZIKV in Bangladesh as local transmission reported by the travelers [68]. Bangladesh is a densely populated country with rapid urbanization which might be also a risk factor for ZIKV [69–71]. Very recently, the endemic Chikungunya virus infection occurred throughout the countries followed by massive Dengue infection. Currently, there is no effective surveillance on ZIKV infections in Bangladesh. Either Zika is circulating and remained to be undiagnosed or it might be next endemic infection in Bangladesh next to the Chikungunya and Dengue virus infections [24,67].

How can we Handle Zika Virus Infection in Bangladesh?

Establishment of national ZIKV surveillance system and laboratory facilities

Government should take immediate steps to establish an effective active surveillance to ensure early detection of the infection which is crucial for the control of the epidemics if any. Whole country need to be covered under such surveillance, especially in *Aedes* prone areas, halftracks, and the border region. To keep the surveillance in action, a high-power ZIKV surveillance and monitoring unit should be formed with relevant experts under the Ministry of Health and Family Welfare. A surveillance unit needs to be set up at the respective immigration area such as in airport, land, and seaport. The ZIKV specific symptoms showed by overseas visitors and having history of travel in Zika endemic region should be tested by rapid Zika diagnosis kit followed by taking necessary action for further confirmation and quarantine. The unit should also keep close liaison with other organizations, professionals, research institutes, hospitals, and Non-Government Organizations. Institute of Epidemiology, Disease Control and Research could play a vital role in Zika surveillance. Engagement of international organizations such as Food and Agriculture Organization (FAO), WHO, and CDC is also crucial for the surveillance activities for logistics and other supports. Establishment of national Arbovirus reference laboratory for ZIKV and other related virus also need to be established following the WHO's algorithm for detecting the viruses (Fig. 3). Veterinarian-physician collaborative research and One Health approach should be conducted to find whether Zika infection is silently circulating in human or domestic animals or non-human primates. Intensive studies of the ZIKV and the possible changes in their genomes/pathogenicity must be reconfirmed, which may reveal genetic and mutational data for updating the fundamentals of the viral biology (Fig. 4) [7,72–74].

Public awareness

The word "Zika" and way of virus transmission should be spread into the mass people by print and electronic media. The community members should be educated regarding their self-protection before, during, and after the travel to a Zika risk area. The traveler especially pregnant women must also be careful during their overseas visit to the Zika endemic regions. The CDC released toolkit for Zika awareness and prevention which includes, CDC-approved messaging, info cards, infographics, a newsletter article, web badges, sample messages for social media, and other materials (https://www.cdc.gov/viajosinzika/pdf/viajo-sin-zika-partnership-toolkit-508.pdf). The social media such

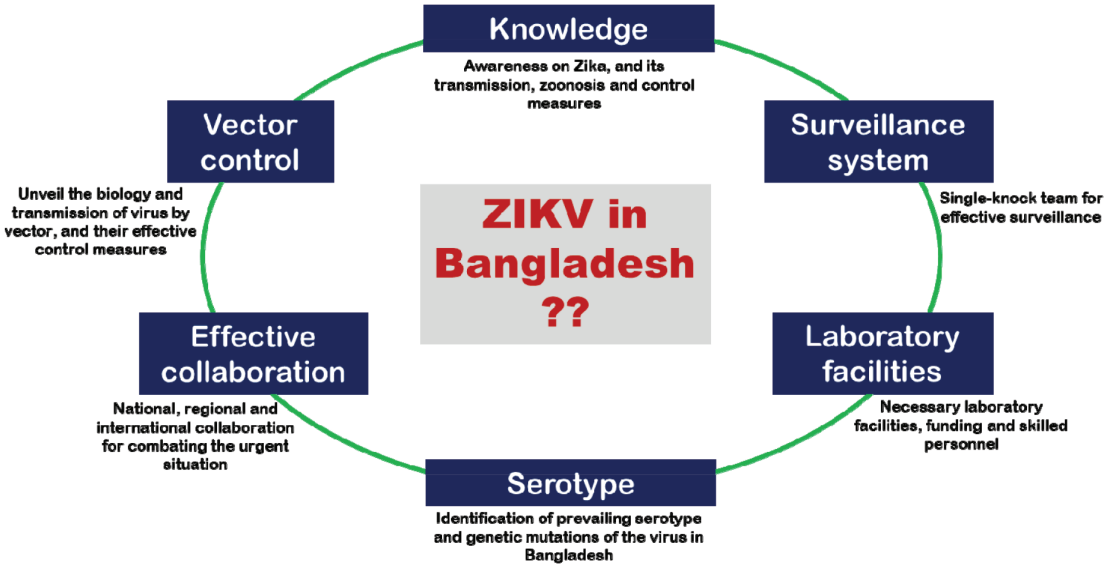

Figure 4. Possible actions need to be adopted to prevent/control Zika from Bangladesh.

as Facebook, Twitter, and Instagram might be the easiest way to campaign message and materials to the mass people regarding Zika awareness and prevention information. Through these social platforms, we need to make sure that individual citizen takes steps to prevent themselves from mosquito bite to protect infections like ZIKV (Fig. 4).

Mosquitoes control

Zika virus is a mosquito-borne virus. Control of mosquitoes is therefore the most important step to control the disease. Since Zika, Dengue, and Chikungunya are transmitted by same vector, i.e., *Aedes* spp., the control strategies for mosquitoes are similar [48]. Integrated mosquito management (IMM) or integrated vector management (IVM) approach to control mosquitoes are in practice in many countries of the world. Local Government needs to make sure that IMM or IVM is practiced in Bangladesh for the control of mosquitoes. These methods allow reducing the mosquito population and thereby reducing the spread of viruses like Zika, Dengue, and Chikungunya. According to CDC, mosquitoes can be controlled by two main strategies; the professional of local government should apply standard action to destroy the larvae and adult's mosquitoes followed by the evaluation of effectiveness. In a recent study from International Centre for Diarrhoeal Disease Research, Bangladesh, it was found that mosquitoes are increasingly getting resistance against insecticides in Bangladesh (https://bdnews24.com/bangladesh/2019/06/27/dhaka-mosquitoes-are-insecticide-resistant-icddrb-study-finds). This is very alarming, as evident from recent outbreak of Dengue in Bangladesh, where in many instances, insecticides used in Dhaka city were not found effective against mosquitoes. On the other hand, around 25 mosquitoes species might be carrier of ZIKV [75]. Therefore, it is necessary to reconfirm the vector biology and transmission of ZIKV considering the geographical perspective of Bangladesh. However, more funding need to be allocated for studying insecticide resistance and reconfirmation of vector biology which will be helpful for developing effective insecticides for mosquitoes control (Fig. 4).

Conclusions and Recommendations

Though ZIKV infection might be asymptomatic or shows mild clinical symptoms, it can be fatal for newborn babies. Adults may also suffer from many neurological disorders due to ZILV infection. On the other hand, ZIKV infection has been reported in almost all the neighboring countries including Bangladesh. Bangladesh is at high risk for emerging threat for ZIKV infection and currently, there is no active surveillance system on it. Therefore, it can be taken into consideration that the recommended actions and strategies illustrated in this short review for the prevention and control of the ZIKV infection in Bangladesh, particularly by establishing national ZIKV surveillance, increase public awareness and mosquito control.

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Nothing to disclose.

Conflict of interests

The authors declared no potential conflict of interests regarding the publication of this article.

Authors' contributions

MGH searched, collected, and reviewed the related articles and prepared the manuscript. KHMNHN and MTR edited and corrected the manuscript. MGH, KHMNHN, SS and MTR revised and finalized the manuscript. All the authors read the manuscript and approved the final version for publication.

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