An Overview of Japanese Encephalitis in Bangladesh

An Undergraduate Research Project (LS 4B06)
Presented to
Dr. Jonathan Dushoff

In Partial Fulfillment
Of the Requirements for the Degree
(Honours) Bachelor of Science
Life Sciences Program

By
Aunima Bhuiya

April 13, 2015
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1. Rationale and context

Japanese encephalitis (JE) is a public health concern among 24 at risk countries in Asia, as shown in figure 1 [1]. JE survivors are associated with long-term debilitating cognitive and physical disabilities, which lead to the heavy burden placed upon families and communities [2]. JE affects all age groups, however JE is most common in children less than 15 years of age [2]. Countries in East Asia including China, Japan and South Korea have seen declines in JE, presumably due to improved socioeconomic conditions and the introduction of JE immunization programs in the 1990s [3]. Currently, these countries have seen 99% reduction in incidence rates following JE vaccines [2]. However, the situation is relatively unclear in low-income countries in South Asia, such as Bangladesh, where reliable estimates of JE burden are not always even available.

![Figure 1. The figure illustrates the geographical distribution of JE. 24 countries in Asia have been identified as areas of JE virus transmission risk. Figure from the WHO [1].](image)

1.1 An International Priority

JE control are aligned with international goals. Firstly, in collaboration with the United Nations Children’s Fund, the WHO developed the *Global Immunization Vision and Strategy* (GIVS). The aim of GIVS is to immunize people and reduce illness and death due to vaccine-preventable diseases by at least two-thirds [2]. Furthermore, JE is a focus within the global targets of the *WHO Global Plan to Combat Neglected Tropical Diseases*. They hope to eliminate JE among low-income countries [2]. This further highlights that JE is an international priority and goal.
1.2 JE Status and Public Health Priorities in Bangladesh

In Bangladesh, the status of JE has only started to be investigated. A novel study that estimated the incidence of JE [4] found rates as high as 2.7 per 100,000 population in the division of Rajshahi (other incidence included 1.4 in Khulna and 0.6 in Chittagong divisions), which are higher to that of Japan before vaccination was introduced (2.5 per 100,000). Thus, there are concerns for the current status in Bangladesh. However, JE may not be able to compete with other public health priorities.

There are other communicable disease priorities in Bangladesh. In 2014, the WHO estimated communicable diseases accounted for almost one-third of total deaths [5]. In 2012, Tuberculosis (TB) was the leading cause of death in Bangladesh [6]. This identifies TB as a high priority in public health. Other communicable diseases that affect the most vulnerable population groups (i.e. children less than 15 years of age) are relatively ignored. The WHO estimated 30% of Bangladesh’s total population are less than 15 years of age [6]. As JE is most common in children, they are more susceptible to long-term disabilities caused by JE.

In 2009, the Institute of Epidemiology, Disease Control & Research (IEDCR) reported that after a consultative meeting on JE prevention and control, it was considered a priority in Bangladesh [7]. However, according to the report titled WHO Country Cooperation Strategy Bangladesh 2014-2017, JE is not explicitly listed as a priority communicable disease that must be addressed in Bangladesh [8]. Its current priority includes other vector-borne diseases such as kala-azar, filariasis and dengue [8]. However, the report mentions the need to reduce the burden of vaccine-preventable diseases. This may allow JE to be considered in the list of priorities by the decision-makers.

This overview explored what is known about JE in Bangladesh, and what still needs to be known to guide public health decision-making.

2. Background

JE is caused by japanese encephalitis virus (JEV), which is spread by mosquitoes (from the genus Culex). JE may result in: 1) asymptomatic JEV infection; or 2) symptomatic JE (clinical) disease [1] (further explained in 2.2 and 2.1.2 respectively). The JEV strain is considered the most important strain as it leads to severe debilitating neurological conditions, with an estimated annual incidence of 50,000 cases [1, 2, 7, 9]. However, with major concerns in poor data collection, JEV infection and JE disease may be underreported, thus resulting in a higher incidence. Furthermore, the case fatality from JE disease may reach up to 35%, which indicates the severity of JE [1, 2, 7, 9].
2.1 Clinical Features

JEV infection in humans produce various clinical manifestations. Various studies report that most individuals with JEV infection are asymptomatic (no symptoms) or cause mild febrile illness (fever of unknown origin), but do not progress to the symptomatic JE disease stage [2, 9, 10]. While it is rare, those who further progress to JE disease have debilitating conditions such as physical, cognitive and psychiatric problems, due to infection of the brain. However, it is not known why developing the disease is rare [9].

2.1.1 Clinical Case Definition

The *WHO Manual for the Laboratory Diagnosis of Japanese Encephalitis Virus Infection* states identifying a case has several stages [10]. First, a patient must be identified as a suspected case with acute encephalitis syndrome (AES), which is an acute onset of fever and a change in mental status (i.e. confusion, disorientation, coma) and/or new onset of seizures [10]. Second, after a suspected case of AES, it is further classified into four groups: 1) laboratory-confirmed JE infection, caused by JEV (as shown in figure 2); 2) probable JE infection, indicating close geographical relationship with another laboratory-confirmed JE case caused by JEV; 3) AES - caused by another agent (bacterial or viral) but not JEV; and 4) AES - suspected case but unknown due to inaccessibility to diagnostic testing [10].

![Figure 2](image.png)

**Figure 2.** Classification of Acute Encephalitis Syndrome (AES) and diagnosing JE from diagnostic laboratory tests. The highlighted boxes indicate the steps to confirm a JE case: 1) individual must be a suspected AES case, 2) cerebrospinal fluid (CSF) obtained, 3) JEV-specific IgM antibodies in the CSF confirm a JE case (further explained in 2.1.2). Modified figure from the WHO laboratory manual [10].

Bangladesh has taken steps to identify JEV infection cases. A prospective hospital-based study found that out of the 176 AES patients recruited into the study, 10 patients were positive
with JEV infection (6% in total) [11]. Other causes of AES included: dengue virus, various viruses in the herpes family (i.e. herpes simplex virus, human parainfluenza viruses, epstein-barr virus,) echovirus. The study raised concern as these were the first confirmed JEV infection cases since the outbreak in Mymensingh in 1977; it was originally thought that the outbreak was localized [11]. Furthermore, after these preliminary results, another hospital-based surveillance study found that among 492 patients that met AES definition, 20 of these were laboratory-confirmed JEV infection (4%). Among JEV-infected patients, 30% suffered from severe neurological damages [12]. While the above studies did not have a large number of JEV infection cases, it highlighted that it is a current concern for researchers to continue to identify the cause of AES in Bangladesh.

As of 2015, the WHO does not have an official number of suspected and confirmed JE cases for Bangladesh.

2.1.2 Laboratory Diagnosis of JEV Infection

Enzyme linked immunosorbent assays (ELISA) are considered the standard method for the diagnosis of JEV infection [10]. The WHO manual for the laboratory diagnosis of JEV [10] states that IgM antibodies specific to JEV are detected from cerebrospinal fluid (CSF) or serum as the sensitivity (how often the test will be positive, given that the patient has JEV) and specificity (how often will the test be negative, given that the patient does not have JEV) are more than 95%. This is usually detected between 7-10 days after reported illness as the WHO indicates that all patients will have JEV IgM antibodies circulating in the body. Furthermore, in order to distinguish JEV from other flaviviruses, an IgM test principle is applied, which includes the following steps: 1) IgM antibody in patient’s CSF bind to ELISA to eliminate non-virus specific antibodies; 2) ELISA plate is washed to remove other immunoglobulins and other serum proteins; 3) JEV antigen is added to bind to JE-specific IgM antibodies; and 4) the use of a detector system that reveals whether JE IgM in the test sample is present or absent. The WHO states that there are other test procedures (i.e. plaque reduction neutralization assay, RT-PCR, virus isolation), however these tests can have lower sensitivity, high associated risk or be time-consuming [10].

2.2 Transmission Cycle

JEV is spread by mosquitoes (from the genus Culex, primarily Cx. tritaeniorrhynchus and Cx. vishnui in South Asia), which breeds in areas with stagnant water (i.e irrigated rice fields). Various reports reiterate JEV transmission cycle includes pigs and ardeidae bird species (i.e. herons, bitterns and egrets) as amplifying hosts (virus multiples inside their body cells), as depicted in figure 3 [1, 2, 4, 9, 10, 13]. While other mammal species may have JEV infection (i.e. cattle), pigs are considered the important amplifying host for transmission to humans, due to the following: 1) high viremia (JEV in the bloodstream) to infect mosquitoes; 2) close proximity
to humans (i.e. pig raising); and 3) high birth rate, which produces a continuous supply of susceptible hosts [2, 9]. Moreover, JEV does not typically cause disease in pigs, however abortions may occur in pregnant sows [2, 9]. For ardeidae bird species, they may help with the geographic of JEV [2, 9].

**Figure 3.** Transmission Cycle of JEV. Infected mosquito bites the animal, and the virus multiplies inside the animal’s body cells (i.e. pig or water bird). An uninfected mosquito bites an infected animal and picks up JEV. Humans are considered dead-end hosts, as they do not have enough viremia to pass on the JEV. Figure from PATH [2].

These assumptions are based on seminal experiments conducted in Japan in the 1950s [14], with further studies showing similar transmission cycles [15-17]. However, studies have tried to determine if other host species are important in the JEV transmission cycle. Van Hurk et al. [9] summarizes that JEV vectors feeding patterns may depend primarily on host availability in the geographic regions. Thus, the transmission cycle may not necessarily coincide in countries where there are low pig population, such as Bangladesh. This is further explored in section 4.2.1.1.

Humans are considered dead-end hosts of JEV, which, while they have viremia, they do not produce enough viremia for mosquitoes to be infected [9]. Thus, humans are unable to pass on JEV.
2.3 Human-targeted Interventions

2.3.1 Vaccination

There are two types of JEV vaccines currently available: 1) inactivated, mouse brain-derived JEV vaccine, and 2) live, attenuated SA 14-14-2 JEV vaccine [2]. Additionally, several other JE vaccines are in late-stage development.

The mouse brain–derived, inactivated vaccine has been available for over 40 years, and has significantly reduced JEV infection burden in Japan, Korea, and Taiwan [9, 18], although vector control and changes in agricultural practices may have contributed to the reduction as well [9]. However, the vaccine has its downfall such as: low compliance (repeated booster shots) in vaccination, complex production process, limited supply issues, safety concerns (e.g. adverse side effects in neurological swelling), and expense. Although the safety concerns are based on limited research evidence, the manufacturer, Biken, discontinued the production of this vaccine, even though the WHO Global Advisory Committee on Vaccine Safety (WHO GACVS) concluded there was no reason to change current immunization recommendations [2].

The live, attenuated SA 14-14-2 vaccine has been use internationally for the last 10 years. It has been demonstrated to be safe and efficacious, low compliance (1 dosage), and has the ability to be coadministered with routine vaccines within the Expanded Program on Immunization (EPI) [2]. Moreover, a cost-effectiveness analysis of JEV control strategies in India estimated this vaccine would cost-effective than the inactivated mouse brain-derived vaccine ($76/DALY in comparison to $1,247/DALY) [2]. As Bangladesh does not have JEV immunization incorporated into their EPI, they may look to neighbouring countries who have introduced a JEV immunization program for guidance in cost-effective interventions. Most recently, the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) has initiated SA 14-14-2 vaccine study for the first time in Bangladesh, in order to determine the safety and the immunogenicity (how it affects the human immune system) in children who have completed all doses in EPI (i.e. routine vaccinations such as measles, polio). This illustrates that Bangladesh is making progress by collecting and analyzing data for WHO prequalification stage in vaccine licensure [19].

2.3.2 Insecticide-treated nets

One study in India found a reduction in JEV incidence by utilizing insecticide-treated nets (ITN) [20]. ITNs act as a physical barrier and prevents access by mosquitoes, thus providing protection against mosquitoes to the individual(s) using the nets. This impedes the transmission cycle of JEV. While there have been no studies on ITNs and its effectiveness against JEV infected mosquitoes in Bangladesh, there have been studies on ITNs being effective against a range of other vectors involved in the transmission of diseases such as leishmaniasis and kala-azar (which are currently listed as high-priority diseases in Bangladesh) [21, 22]. Thus,
ITNs may be a possible cost-effective intervention for JEV transmission while researchers continue to understand its impact within Bangladesh.

2.4 Vector Control

It has been generally accepted that vector control for JEV has limited effectiveness and practicality in most settings [1, 2, 9, 13]. The reasoning behind this involves mosquito control being resource intensive and have associated high costs [9]. These coupling factors may not necessarily allow for vector control to be an option resource limited countries such as Bangladesh. Moreover, one study found that the extensive irrigated rice agriculture that provide habitats for *Cx. triaeniorhynchus* and *Cx. vishnui* and the isolated rural villages made it difficult to apply large-scale chemical treatment. Furthermore, the study reached concerns of the alteration of the ecology in the surrounding area, such as the niches and food webs [9]. However, the identification of these alterations are beyond the scope of this literature review.

2.5 Pig-targeted Vaccination

Various studies have been done to determine the effectiveness of pig-targeted vaccination on controlling JEV transmission. One study found that pig vaccination is not effective for preventing transmission to humans due to a high turnover of pigs (slaughtered at 6-8 months of age) and maternal antibodies render the live-attenuated vaccine ineffective [23].

However, a recent study in Bangladesh found a potential benefit to pig-targeted vaccinations [24]. A model of JEV transmission in pigs estimated that by vaccinating half of the pig population in the districts of Rajshahi, Nawabgonj and Naogaon, it may result in an 82% reduction of JEV infection incidence in pigs [24]. Unfortunately, it is not straightforward to suggest that pig-targeted vaccination is effective, as the study also pointed out the results were under several assumptions, which include life-long immunity (following JEV infection), JEV epidemic is at steady state in pigs and vaccine efficacy rate of 95%. Thus, vaccinating pigs could be a possible short-term control of JEV, considering Bangladesh is in between the stages of understanding JEV transmission and preliminary human vaccine licensure. However, considering the high turnover of pigs and the uncertainty in the efficacy of pig-targeted vaccination, it may not be in Bangladesh’s best interest to pursue this method of JEV control in the long-term, where more effective prevention interventions are available and cost-effective.

3. JEV-specific research priorities and challenges in Bangladesh

3.1 Surveillance & Sentinel Surveillance

The following sections describe what is known about sentinel surveillance in Bangladesh and what Bangladesh can learn from India with its expansion of JE sentinel surveillance.
Surveillance involves the ongoing collection, analysis and dissemination of data that is essential to the planning and coordination of public health programs such as immunization [25]. As a subtype, sentinel surveillance is frequently used when high-quality data are needed about a certain disease in the country. This subtype is commonly used in resource limited countries (i.e. lack of central reporting system, shortage of health professionals), where it is difficult to collect reliable data [25]. Specifically, JE sentinel surveillance sites are selected based on WHO standards, which include: 1) high probability of suspected cases of AES, 2) and the access to high-quality laboratory facilities and well-qualified staff [25]. Data collection from these sites can signal transmission trends in these regions and indicate to health ministers the need for expanded surveillance [25].

3.1.1 Limited Sentinel Surveillance

Bangladesh has limited sentinel surveillance. Along with the WHO and CDC, the director of the Institute of Epidemiology, Disease Control and Research (IEDCR), Dr. Mahmudur Rahman [7], established an acute (meningo-) encephalitis surveillance (AMES) as the standardized mechanism to identify the causes of viral encephalitis in Bangladesh. AMES is established in only 3 hospitals in Bangladesh; these are located in the divisions of Rajshahi, Chittagong, Khulna, as depicted in figure 4 [7]. For context, Bangladesh has a total of 7 divisions. Thus, it seems reasonable to suppose that, geographically, there is limited laboratory capacity to identify JEV infection cases, as there are currently no other AMES sites in the other 4 divisions situated in Bangladesh, including Dhaka - the most populous division.

Figure 4. Sentinel Sites in Bangladesh, in the divisions of Rajshahi, Khulna, Chittagong and its shaded catchment area. Modified figure from Paul et al. [4].
Furthermore, since the establishment of AMES sites, there has only been one published study that utilizes these sentinel sites as a source of data collection and analysis. In a novel study on the estimation of JE incidence among the catchment area of Rajshahi, Chittagong and Khulna AMES sites, Paul et al. [4] determined 11 districts that met their catchment criterion. The primary catchment area criterion included districts where the suspected AES patients resided before admittance to the hospitals. The study identified 17 of the 267 encephalitis cases was caused by JEV [4] The small sampling may not reflect the actual number of encephalitis cases and subjected to underreporting bias [3]. Two WHO reports indicated limited surveillance is a hindrance to identifying the magnitude and burden of JE, as well as the transmission trends in specific areas of Bangladesh [1,3]. And so, the unknown status of JE burden bears a potential barrier for policy-level decision making on prevention interventions.

3.1.2. Learning from India

The current status of JE burden in India is beyond the scope of this literature review. However, Bangladesh could learn from India’s past outbreaks in order to further support the expansion of sentinel surveillance. Parida et al. [26] determined that in 2005, JEV was the cause of thousands of cases and deaths during a severe outbreak of encephalitis in Northern India. The nation established 50 WHO-standardized sentinel sites in order to better respond to outbreaks [2]. Furthermore, a recent report suggested that the ongoing collection and analysis of data allowed India to initiate JE vaccination campaigns to immunize vulnerable populations in 179 districts [2]. However, sentinel surveillance in India is nowhere near perfect. Tiwari et al. [27] suggests that there is a possibility that many cases are unreported due to various reasons (i.e. limited access to sentinel site, JE underrecognition) and the true magnitude may be substantially higher, similar to Bangladesh. Unfortunately, it is not straightforward to relate JE burden between India and Bangladesh (partly because of differences in socioeconomic and geographical distribution). However, India’s experiences with vaccine introduction may be important for spreading the message about JE among stakeholders at the policy level in Bangladesh.

3.2 Determinants of JEV transmission

Determinants associated with the JEV transmission cycle are not well understood. The following section describes factors that are commonly mentioned in literature about JEV transmission (such as amplifying host species), but specifically, what is currently known and unknown for Bangladesh.

3.2.1 Potential Amplifying Host: Pigs

There is limited evidence to suggest pigs are the key species in JEV transmission in Bangladesh. One recent study in a JEV-endemic region identified 11,364 pigs, and tested 312 for JEV antibodies [24]. They found that among the tested pigs, 30% had evidence of seropositivity;
in other words, these pigs were positive for JEV in their serum. However, there are limitations to this study. First, it is difficult to compare the results with other studies in Bangladesh because this is the first field study about JEV transmission among pigs. Second, the study does not identify other possible host species from which JEV may have originated from instead [24]. Thus, there is not enough evidence to identify pigs as the major host species. The study’s recency indicates that researchers have started to confront JE in Bangladesh. Further research may help define the role of pigs in JEV transmission in Bangladesh.

Furthermore, descriptors of the pig population (i.e. species, distribution by division) is relatively unknown and have not been explored in detail in Bangladesh. The Bangladesh Department of Fisheries and Livestock conducted a census to estimate domestic pig population and its distribution by division, but until March 2015, there is no published data available [28]. This poses an issue when conducting data collection on the JEV seropositivity prevalence among pigs. However, some recent studies identified pig population among the districts in Dhaka, Rajshahi and Chittagong, to a total in the thousands [24, 28, 29]. There may be other pig populations to be discovered in other divisions and districts and has become a research priority for ICDDR,B [7].

However, there are some barriers to identifying the interaction between pigs and people in Bangladesh. A recent study found there are two main ways of raising pigs in Bangladesh: 1) by indigenous communities raising pigs in their backyards, and 2) by pig herders [28]; however, they found difficulties in data collection when identifying pig herders due to their frequent mobility. Moreover, the difficulty to access indigenous communities and pig herders is another barrier. The study found that this population are severely stigmatized due to their association with pigs (Bangladesh’s population is predominantly Muslim), and often distrust anyone outside of their community [28]. Thus, future qualitative researcher must establish trust among these marginalized communities in order to understand pig and human interaction for JEV transmission.

3.2.2 Potential Amplifying Hosts: Ardeidae Birds

The role of birds from the family Ardeidae (i.e. herons, bitterns and egrets) for JEV transmission in Bangladesh are not clearly defined. Various reports seem to establish ardeidae birds as an amplifying host species [1, 2, 3, 7, 9, 13]. However most of what is known about ardeidae birds role in JEV transmission comes from field studies conducted between 1959 to 1997 [14-17]. Van Hurk et al. [9] summarized that during a five-year study period, JEV strains were discovered in herons and egrets; subsequent laboratory experiments confirmed the high levels of viremia was sufficient to infect JEV vectors such as Cx. triaeniorhynchus. A more recent serological study in a JEV endemic region found similar results with JEV infection in ardeidae bird species (i.e. pond herons, egrets) to that of the field studies [30].

Although ardeidae species role in JEV transmission has been studied, it remains unclear on its implications in Bangladesh. Besides the fact that 17 ardeidae species originate from
Bangladesh [31], there is no research to implicate its role in JEV transmission in the nation. There is promise in ardeidae species research as ICDDR,B has highlighted its priority [7].

3.2.3 Other Amplifying Hosts to Consider

There is a possibility that there may be other amplifying hosts that haven’t been considered by researchers, such as the cattle and chickens in Bangladesh. The role of cattle as a potential amplifying host of JEV transmission is not clearly understood. Arunachalam et al. [32] observed JEV vector *Cx. tritaeniorhynchus* fed more on cattle than pigs, however they found a higher population of cattle than pigs in the region. This is the case in Bangladesh, where cows are a huge population in livestock, with an estimated 25,150,000 cattle, while there are limited number of pigs [33]. However, some reviews of studies [9, 13, 24, 34] assume cows do not demonstrate viremia (JEV in the blood), which is needed to infect mosquitoes and continue the transmission cycle. Yet, one study found JEV infections are common in cattle and may circulate in the blood [35]. Therefore, with mixed results found from limited studies, it is unclear if cattle play an important role in JEV transmission.

In Bangladesh, the second largest livestock population is that of chickens. Chickens are among birds that develop low viremia, however a recent study indicated that hatched chicks develop viremia high enough to infect *Cx. tritaeniorhynchus* [36]. In Bangladesh, free range chickens are very common throughout all the divisions, which live and breed near humans. This may provide a continuous supply of amplifying hosts for JEV.

Thus, Bangladesh may want to consider cattle and chickens as potential amplifying hosts of JEV.

3.2.4 Environmental Determinant: Irrigated Rice Agriculture

Another potential determinant of the JEV transmission is the relationship between the JEV vector species and irrigated rice agriculture. Various studies have been done in great detail to determine the ecology of JEV vector species and its preferred larval habitats in rice fields [KEI]. However, the presence of rice irrigation and vector abundance in relation to human JEV infections have not been researched in Bangladesh. For comparison, Kanojia et al. [37] analyzed northeast divisions in India (that have extensive irrigated rice agriculture) and found that a high occurrence of human JEV infections was closely associated with high vector densities that were breeding in the rice fields. And in another study, humans involved in rice field cultivation and households close to these water bodies were found to be factors associated in recent JEV infections in northeast divisions [38]. Considering, 82% of Bangladesh’s population live in close proximity to irrigated rural areas, this environment determinant may play a key role in JEV transmission throughout the nation [3].
3.3 Bangladesh’s Health System

Bangladesh’s health system is inadequate to address the needs of vulnerable population groups. First, the nation faces shortages of health professionals (i.e. doctors, nurses), a disarrayed public health sector, and improper healthcare resource allocation between the public and for-profit private sector [39-41]. Second, the government only spends 3.7% of its GDP on healthcare, which leaves an inadequate public health sector and a growing for-profit private sector in order to compensate for the gaps in the health system [39, 40]. Thus, the culmination of these issues results in the inequity of healthcare access, specifically in rural areas where JEV infections are said to be a concern.

3.3.1 Potential Challenges to JE Research

There are potential barriers to JE research in Bangladesh. First, the WHO categorizes Bangladesh as a “health workforce crisis country”, as there are less than 3 health professionals for every 10,000 people in the country [41]. The lack of qualified and trained health professionals may lead to insufficient knowledge and identification of encephalitis cases caused by JEV. Second, the public health sector usually caters to impoverished people; however, the sector is suffering from inadequate hospital infrastructure in the rural areas [39, 41]. Last, for-profit private hospitals that have laboratory capacity for JE diagnosis, are disproportionately clustered in urban areas [40]. The inadequate infrastructure and proliferation of for-profit private hospitals creates limited allocation of resources [41]. A hospital-surveillance study found that the distance from a rural village to a sentinel hospital is a contributing factor in seeking JE diagnosis and treatment [12]. Thus, in the future, this may limit the distribution of AMES sentinel sites and JE diagnostic capacity, especially in rural areas. Consequently, this may allow gaps in the health system, where JEV infections may be unreported.

4. What are the next steps?

From a public health perspective it is essential to continually identify, assess and monitor the progression of JE. Bangladesh may continue to: 1) monitor and expand surveillance sentinel sites and laboratory capacity; 2) identify geographical areas at high risk of JE; 3) identify potential amplifying hosts; and 4) identify the efficacy and safety of the JE vaccine in Bangladeshi children [2]. The following questions need to be addressed in order to further tackle the issue:

1. What is the JE burden in Bangladesh?
2. What is the geographical distribution of JE among the divisions and districts in Bangladesh? Which division is most affected?
3. What are the amplifying hosts in Bangladesh?
4. How can we strengthen Bangladesh’s health system in order to ensure appropriate cost-effective interventions are taken to consideration?
Limitations

Due to the limited studies, it was impossible to determine the magnitude and burden of JE in Bangladesh. Moreover, there is no data on the confirmed JEV infection cases and JE disease cases by the WHO. Thus, the status of JE in Bangladesh is relatively unknown. However, the recent studies in Bangladesh indicate that there is a growing interest to determine the prevalence of JE. Therefore, further studies are needed.
Appendix

Article Search
The articles included in this literature review were identified by keyword searches in the PubMed, Web of Knowledge, WHO, Health Systems Evidence, Health Evidence databases. Additionally, general google scholar searches were conducted. Combinations of keywords “Japanese encephalitis”, “encephalitis”, “Bangladesh”, “vaccination”, “incidence”, “health system”, “surveillance”, “data”, “transmission”, “south asia” were used to identify relevant articles. Abstracts were then reviewed to ensure that articles met certain criteria for inclusion: (1) publication date between 2004 and 2014, (2) addressing encephalitis or Japanese encephalitis in south asia, (3) Bangladesh as the country of interest. The rationale behind examining articles from 2004 to 2014 was to provide an update on previous efforts to understand causes of viral encephalitis and JEV, such as the prospective hospital-based surveillance study by Center for Health and Population Research (ICDDR, B) and the Centres for Disease Control and Prevention (CDC) in 2004 [SUR]. Additionally, recent articles should reflect the current methodological advancements and status of JE in Bangladesh. Furthermore, studies before 2004 were included to provide context to what was studied about JE during its first emergence.
References


