Short Report: Dengue Virus and Japanese Encephalitis Virus Epidemiological Shifts in Nepal: A Case of Opposing Trends

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Abstract. We report on the changing epidemiology of two important flaviviruses in Nepal: Japanese encephalitis (JE) and dengue viruses. Morbidity and mortality in Nepal is in the thousands since JE was introduced in 1978. Nepal launched an extensive laboratory-based JE surveillance in 2004. Nepal experienced a remarkable reduction in disease burden after mass immunizations from 2005 to 2010, when 2,040 JE infections and 205 JE-related deaths were confirmed. With its emergence in 2006, dengue has become a significant challenge in the country, highlighted by a sudden outbreak in 2010 that resulted in 359 confirmed dengue infections. Currently, both viruses cocirculate in Nepal. Here, we document the remarkable expansion of dengue in Nepal, which urgently requires national surveillance to refine the burden and make recommendations regarding control and prevention programs. We believe that the use of existing JE surveillance network for integrated dengue surveillance may represent the most appropriate alternative.

Japanese encephalitis (JE) and dengue viruses are two important flaviviruses causing significant morbidity and mortality globally. Vaccine availability and widespread use coupled with vector control measures have significantly reduced JE burden in developed countries,¹ although persisting problems exist in developing countries with limited or no vaccine coverage. Unlike JE, dengue lacks licensed vaccines, making it a major public health problem; at least 2.5 billion people are at risk, and there are 100 million infections each year and considerable economic, political, and social costs worldwide.^{2–4}

Nepal, a Himalayan country surrounded by India and China, reported the introduction of JE into the country from the neighboring northern states of India as early as 1978. Since then, several major JE outbreaks left 26,918 infections, including 5,369 deaths as of 2004.^{5,6} In response, the Ministry of Health and Population in Nepal started systematic laboratory-based surveillance of JE in mid-2004 using World Health Organization (WHO)-recommended standards,⁷ likely the most extensive JE surveillance activity in the region.⁸ The JE surveillance network gradually expanded to include 11 surveillance field offices, 126 reporting hospitals, and 85 active surveillance sites in the country as of 2010. Unfortunately, a similar dengue surveillance network in Nepal does not exist, despite its proximity to endemic areas and the increasing intra-regional trade and tourism.³ Nepal experienced its first dengue outbreak in 2006, nearly three decades after the introduction of JE. Dengue infections were then confined to a few districts, underscoring the nascent nature of the virus in the country and its potential for expansion.^{9,10} A small (5.4%) proportion of cases (from 2004 to 2005) of measles-like illness outbreaks was presumptively dengue by serological testing, but there was no additional confirmation.¹¹ Currently, both JE and dengue viruses cocirculate in Nepal. In this report, we highlight the changing epidemiology of these two flaviviruses in Nepal from 2005 to 2010, specially focusing on the emer-

gence of dengue and the need to increase surveillance through integration into the existing JE surveillance system.

Description of the Nepal JE surveillance methods is described elsewhere.⁸ Briefly, patients with acute onset of fever and deterioration in mental status (e.g., confusion, disorientation, coma, or inability to talk) and/or seizures (excluding febrile seizures) were defined as acute encephalitis syndrome (AES) cases.^{7,8} Referral hospitals within the surveillance network captured the AES/JE cases throughout the country. As a part of the JE surveillance, AES acute serum and/or cerebrospinal fluid specimens were transported to and tested at the National Public Health Laboratory (NPHL) for the presence of anti-JE virus immunoglobulin M (IgM) by a reference IgM capture enzyme-linked immunosorbent Assay (ELISA).¹² Specimens with IgM titers of 40 units or above were considered JE-positive. Negative specimens were not further tested and designated as AES of unknown etiology. NPHL also serves as the study center for dengue and other associated illnesses and coordinates a network of government and private hospitals/laboratories throughout Nepal. Despite the lack of active dengue surveillance activity, data collection was consistent throughout the investigation of dengue suspected cases captured at nine selected tertiary care hospitals until the end of 2010. Any suspected clinical dengue cases as based on the WHO guidelines¹³ were further investigated. Clinical dengue cases included acute febrile patients presenting two or more of the following symptoms: headache, retro-orbital pain, myalgia/arthralgia, nausea/vomiting, and skin rashes. Specimens were then screened for dengue virus at the collection sites and later confirmed at NPHL by dengue-specific IgM and IgG ELISA (Standard Diagnostics, Kyonggi-do, Korea) followed by immune response determination as described previously.¹² Briefly, IgM:IgG ratios of ≥ 1.8 and < 1.8 were considered as primary dengue infections or secondary dengue infections, respectively. To eliminate the possibility of cross-reactivity with JE, specimens were also tested by anti-JE virus IgM capture ELISA as described above.¹²

During the period of 2005–2010, 2,040 confirmed JE cases and 205 deaths were reported in Nepal. JE cases were reported from 62 of 75 districts of the country (Figure 1). The

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FIGURE 1. Geographical distribution pattern reflecting cocirculation of dengue and JE in Nepal, 2005–2010.

trend of JE cases and deaths showed a notable reduction after 2005 (Figure 2). This reduction directly correlates with JE immunization in the country. Following the recommendations of the JE surveillance report, a general immunization plan was put forward⁸ which was also supported by the evidence of high level of protection conferred by JE vaccine in Nepal.^{14–16} The mass immunization campaign was launched

with live attenuated JE vaccine (SA 14-14-2) in selected high-risk districts in 2006. In 2009, JE vaccine was included in the routine immunization schedule in 17 endemic districts that completed previous catch-up campaigns.¹⁷

Although the initiation of routine immunization has increased hopes for controlling JE, the recent emergence of dengue has stood as another big challenge for disease control programs in

FIGURE 2. Dengue and JE trends in Nepal, 2005–2010. Numbers indicate recorded cases of JE infections (blue line), JE deaths (red line), and dengue infections (black line) per year. Arrows indicate JE immunization campaigns. Confirmed dengue cases started from 2006,⁹ because the clinical dengue cases in 2005 lacked confirmation.¹¹

Nepal. After the first outbreak in 2006, there was very little dengue activity in the country during 2007–2009 (2, 8, and 16 confirmed infections per year, respectively) (Table 1). However, a large outbreak in August to December of 2010 resulted in at least 359 confirmed dengue infections among 1,215 clinical cases (30%). The major epicenters of this outbreak were two lowland terai districts in the southern tropics (Chitwan and Rupandehi) of central and western Nepal, respectively. Overall, 12 of 75 districts reported confirmed dengue throughout this outbreak, including four hill districts located north of the terai.

Among the confirmed 2007–2010 dengue cases, most were male (both in children and adults). This might be because males have higher vector exposure or better access to hospitals and other healthcare facilities.⁹ During the study period, the median age of the dengue patients remained between 28 and 31 years. Overall, the majority of the dengue infections occurred in adults, and the proportion of confirmed infections in children (< 15 years) was reported to be up to 13% (47/359). Higher frequency of dengue in adults may be associated with the lack of immunity in adults living in areas where dengue was introduced only recently. Compared with primary infections, secondary infections were observed in relatively larger numbers of patients during the period. This observation is also consistent with the circulation of multiple serotypes in the country during the first outbreak in 2006, although we cannot discount the possibility of earlier undiagnosed or asymptomatic infections.⁹ The high proportion of secondary dengue cases may come from residents of the southern terai districts, bordering India's northern states where dengue is endemic.¹⁸ People movement across the border in this area is extensive, creating ample opportunity to acquire the disease. Over the past 4 years, dengue has been confirmed in 14 districts, including 9 districts without previous dengue reports. With this recent expansion, the total number of districts with confirmed dengue infections in Nepal has reached 18, almost all among the urban and semiurban or densely populated rural areas with tropical climate (Figure 1).

Although *Aedes albopictus* was reported in Nepal's southern plains during the 1980s, *A. aegypti* (the major dengue vector) was first identified during the 2006 dengue outbreak in urban areas of the terai districts but not in the hill areas like Kathmandu.^{9,19} *A. aegypti* was first reported in Kathmandu in 2009.²⁰ Recently, significant numbers of both vectors have also been identified in Kathmandu during a 2012 survey conducted by the District Public Health Office (personal communication). Emergence and expansion of the dengue virus in Nepal correlate with these entomological findings, suggesting potential future epidemics. However, additional investigations are required to understand the transmission dynamics at the molecular level.

Most of the areas with reported dengue infections are also endemic for JE, requiring improved differential diagnosis in the existing guidelines in the country.³ Cross-reactivity cannot be totally excluded. However, we think cross-reactivity is less likely, because dengue specimens were also tested for anti-JE virus IgM, and seven samples with positive serology for both dengue and JE were excluded from the data analysis. In addition, seasonality, locality, past outbreak history, and presence of vectors were also carefully examined during the investigation. Despite these efforts, we may not be able to rule out cross-reactivity while using antibody-based detection techniques, because samples from AES cases were tested for neither dengue nor etiologies other than JE. However, detection of anti-JE IgM antibodies remains adequate for surveillance purposes according to the WHO guidelines.⁷

Although the JE data presented here are derived from extensive national surveillance, we are restricted to dengue data from NPHL and limited government facilities. Moreover, paired sera were not available from all the patients, and false-negative results can be expected, especially when acute serum specimens are collected soon after onset of symptoms. Some dengue patients with neurological signs might have been missed, because we did not test JE-negative samples for dengue. Because of these factors, dengue is likely underreported. Nevertheless, the data collected as of 2010 are

TABLE 1
Dengue in Nepal, 2007–2010

Parameters	Outbreak period			
	2007: sporadic	2008: sporadic	2009: September to October	2010: August to December
Total cases				
Clinical dengue	10 (100)	25 (100)	35 (100)	1,215 (100)
Confirmed dengue	2 (20)	8 (32)	16 (46)	359 (30)
Children (< 15 years)				
Clinical dengue	2 (100)	3 (100)	3 (100)	177 (100)
Confirmed dengue	0 (0)	0 (0)	1 (33)	47 (27)
Age in years (confirmed dengue)				
Range	26–30	20–35	20–68	2–87
Median	28	27	31	28
Sex (confirmed dengue)				
Male	1 (50)	6 (75)	11 (69)	230 (64)
Female	1 (50)	2 (25)	5 (31)	129 (36)
Infection type*				
Primary	1 (50)	2 (25)	6 (37)	112 (40)
Secondary	1 (50)	6 (75)	10 (62)	167 (60)
Number of districts with confirmed dengue				
Terai	1	2	3	8
Hill	0	1	2	4
Total	1	3	5	12

Dengue in 2006 (the first outbreak) has been described previously,⁹ whereas the clinical dengue cases in 2005 lacked confirmation.¹¹ Figures in the parenthesis are percentages.

*During 2010, paired sera were available from only 279 of 359 dengue-positive patients.

sufficient to believe that dengue is expanding in Nepal, coinciding with the decrease in JE incidence.

To the best of our knowledge, in addition to JE, infection rates of other flaviviruses (except for a few dengue reports) in Nepal have not been well-documented. Because a campaign of immunization against JE is underway, now it is time to increase attention to dengue, a newly emerged disease in Nepal. With the sudden upsurge in dengue cases observed, there is an urgent need for laboratory-based surveillance to accurately assess the disease burden and make recommendations regarding appropriate control and prevention. The use of existing facilities is crucial in reducing the cost and time of dengue surveillance. This approach was followed in the successful infrastructure, data management, and specimen transportation integration of diseases surveillance (including JE) into the pre-established acute flaccid paralysis (AFP) surveillance in Nepal.⁸ Similar integration approach is equally useful in the context of prompt development of dengue surveillance system in the country. We believe that the use of the existing national JE surveillance will bring about more accurate dengue surveillance, providing a cost-effective and easy-to-implement platform.

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