Estimation of the Impact of a Japanese Encephalitis Immunization Program with Live, Attenuated SA 14-14-2 Vaccine in Nepal


Abstract. Wider availability of the live, attenuated SA 14-14-2 Japanese encephalitis (JE) vaccine has facilitated introduction or expansion of immunization programs in many countries. However, information on their impact is limited. In 2006, Nepal launched a JE immunization program, and by 2009, mass campaigns had been implemented in 23 districts. To describe the impact, we analyzed surveillance data from 2004 to 2009 on laboratory-confirmed JE and clinical acute encephalitis syndrome (AES) cases. The post-campaign JE incidence rate of 1.3 per 100,000 population was 72% lower than expected if no campaigns had occurred, and an estimated 891 JE cases were prevented. In addition, AES incidence was 58% lower, with an estimated 2,787 AES cases prevented, suggesting that three times as many disease cases may have been prevented than indicated by the laboratory-confirmed JE cases alone. These results provide useful information on preventable JE disease burden and the potential value of JE immunization programs.

INTRODUCTION

Japanese encephalitis virus (JEV) is the most common vaccine-preventable cause of encephalitis in Asia.1 Of an estimated 67,900 cases of Japanese encephalitis (JE) annually, approximately 20–30% are fatal, and 30–50% of survivors have neuropsychiatric sequelae.2 JEV is transmitted in an enzootic cycle between mosquitoes and amplifying vertebrate hosts, primarily pigs and wading birds, and it is spread to humans through the bite of an infected mosquito.

In recent years, the improved availability of JE vaccines has resulted in substantial progress in control of JE. Wider international availability of the live, attenuated SA 14-14-2 JE vaccine, in particular, has facilitated introduction or expansion of JE immunization programs in India, Nepal, Cambodia, the Democratic People’s Republic of Korea, and Sri Lanka. The SA 14-14-2 JE vaccine is manufactured by the Chengdu Institute of Biological Products in China. Since the vaccine was first licensed in 1989, more than 200 million children have been vaccinated in China, and over 90 million doses have been used in other countries. The vaccine is considered safe, affordable, and effective.3–6 In a study in Nepal, 96% effectiveness was shown 5 years after administration of a single dose.7 However, no studies have been published that clearly describe the impact of an immunization program using this vaccine.

JE has been recognized as a public health problem in Nepal since the mid-1970s, when cases were first reported from the Terai region in the south.38 In 2006, the Ministry of Health and Population (MOHP) in Nepal launched a national JE immunization program. By 2009, mass campaigns had been conducted in 23 districts with the highest JE disease burden. Routine JE immunization for children aged 12–23 months was introduced in one of these districts in 2008 and an additional 15 of the remaining 22 districts in 2009. A single dose of SA 14-14-2 JE vaccine was used both in campaigns and the routine program. We analyzed routine surveillance data collected from 2004 to 2009 to describe the impact of the JE immunization program in Nepal.

METHODS

Setting. Nepal is comprised of three ecological regions—the Terai (plain), hill, and mountain regions—that span the country from west to east and increase in altitude from south to north. Among Nepal’s population of approximately 27 million people, about 47% live in the 24 districts of the Terai region. This lowland region has high annual rainfall and extensive rice cultivation, providing ideal conditions for the breeding of Culex mosquitoes, the principal vectors for JEV. Pigs are also common and often reared in close proximity to humans.10 These favorable conditions for JEV transmission have resulted in high disease burden in the Terai region, with large outbreaks typically occurring at intervals of about 2–4 years.11 The first documented outbreak of JE in the hill region occurred in the Kathmandu Valley in 1995, and later studies confirmed JE endemcity there.12–14 In recent years, JE cases have been reported at increasing frequency from additional hill and mountain districts.15

Mass immunization campaigns were conducted in 23 (31%) of Nepal’s 75 administrative districts from 2006 to 2009. Campaigns commenced in the six Terai districts with the highest JE disease burden and by 2009, had been implemented in 20 (83%) of 24 Terai and 3 (9%) of 35 hill districts. Campaigns targeted children aged 1–15 years (11 districts) or all persons aged ≥ 1 year (12 districts). Adults were vaccinated in some districts because surveillance data indicated that as many as 50% of JE cases in Nepal occurred in those individuals > 15 years.11,16 A communication strategy was implemented to encourage participation in the campaigns, and vaccines were available free of charge at health clinics. The median reported campaign coverage rate was 94% (range = 81–115%). District coverage estimates higher than 100% may...
have been because of underestimates of a district’s population or residents of other districts being vaccinated and included in tallies.

For this analysis, the campaign districts were allocated into JE risk categories based on historical levels of endemicity. Four western Terai districts with high seasonal JE incidence rates (Kailali, Bardiya, Banke, and Dang) were classified as high risk; the 19 remaining districts with recurrent seasonal JEV transmission but lower incidence rates were classified as moderate risk.

**Acute encephalitis syndrome and JE surveillance in Nepal.** Reporting of acute encephalitis syndrome (AES) cases commenced in Nepal in 1978. AES/JE surveillance was strengthened in 2004 with designation of 45 medical facilities as sentinel sites, enhanced case-based surveillance using a standardized case definition, improved access to JE laboratory testing, and use of the infrastructure developed for polio surveillance. The initial 45 sentinel sites consisted of 34 sites in 20 of 24 Terai districts and 11 sites in 5 hill districts. The AES/JE surveillance system was expanded to additional sites in subsequent years. However, for consistency, in this analysis, data from only the original 45 reporting sites were used.

AES cases identified at sentinel sites are reported by surveillance medical officers to the Programme for Immunization Preventable Diseases at the World Health Organization (WHO) in Nepal. Samples of cerebrospinal fluid (CSF) and/or serum are collected when possible and tested at the National Public Health Laboratory or B. P. Koirala Institute of Health Sciences laboratory using the Armed Forces Research Institute of Medical Sciences JE immunoglobulin M (IgM) antibody capture (MAC) enzyme-linked immunosorbent assay (ELISA). Epidemiological and laboratory data are entered into an MOHP/WHO database.

**Surveillance case definitions.** In accordance with WHO-recommended surveillance standards, an AES case is defined as a person of any age in any geographical region at any time of the year with the acute onset of fever and a change in mental status and/or new onset of seizures, excluding simple febrile seizures. All cases that meet this definition are included in clinical AES surveillance, regardless of whether laboratory testing is conducted. A JE case is defined as an AES case with JEV-specific IgM antibody in a sample of CSF or serum detected by a MAC ELISA.

**Data analysis.** Expected and observed AES and JE cases and incidence rates were compared. The expected incidence rates were determined by calculating the incidence per 100,000 person-years in each district or age group before the vaccination campaign. This rate was applied to the relevant population after the vaccination campaign, which provided the expected number of cases had the campaign not occurred. The observed cases were those cases reported after the immunization campaign, and the observed incidence rate was the number of reported cases per 100,000 person-years post-campaign. The differences between expected and observed incidence rates were calculated. Exact binomial confidence intervals were used.

In each district, the cut-off date between the pre- and post-vaccination campaign periods was determined by selecting the midpoint of the vaccination campaign and adding 2 weeks to allow for development of immunity after vaccination. Campaigns were typically completed over a period of 2 weeks to 2 months, but in three districts, partial campaigns were conducted in 2 consecutive years. To provide a conservative estimate of impact in these districts, the same definition for the cut-off date was applied in the first year of the campaign. In summary, cases used to calculate expected incidence rates were those cases that occurred from 2004 until 2 weeks after the midpoint of the vaccination campaign, and observed cases were those cases that occurred > 2 weeks after the midpoint of the campaign until the end of 2009.

Denominator data for incidence calculations were obtained from the Nepal Department of Health Services’ Health Management Information System and are official population estimates used by the Nepal MOHP. The available age group data were limited to < 1, 1–4, 5–14, and ≥ 15 years categories. SAS version 9.2 (SAS Institute, Cary, NC) was used for data analysis.

The protocol was reviewed by the MOHP in Nepal and the US Centers for Disease Control and Prevention and considered to be a program evaluation. Therefore, Institutional Review Board review was not required.

### RESULTS

**Impact on JE incidence and cases.** In the 23 districts that implemented immunization campaigns, the observed post-campaign JE incidence rate of 1.3 per 100,000 population was 72% lower (95% confidence interval [CI] = 69–75%) than the expected incidence of 4.6 per 100,000 (Table 1). An estimated 891 (95% CI = 855–930) JE cases were prevented by the vaccination campaigns. Among the 23 districts, the expected versus observed incidence showed a significant decline in 10 (43%) districts and no significant change in 13 (57%) districts. The median difference between observed and expected incidence was 48% lower (range = 100% lower to 67% higher).

The greatest impact was seen in the four high-risk Terai districts, where the observed incidence rate was 84% lower (95% CI = 81–86%) than expected. In the moderate risk areas, the observed post-vaccination incidence was 45% lower (95% CI = 36–52%) in the 16 Terai districts and 43% lower (95% CI = 7–67%) in the 3 hill districts.

### Table 1

<table>
<thead>
<tr>
<th>Area</th>
<th>Campaign target population</th>
<th>Campaign year</th>
<th>Expected Cases</th>
<th>Expected IR</th>
<th>Observed Cases</th>
<th>Observed IR</th>
<th>Difference in IR (%)</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated districts (N = 23)</td>
<td>Variable</td>
<td>2006–2009</td>
<td>1,240</td>
<td>4.6</td>
<td>349</td>
<td>1.3</td>
<td>−72</td>
<td>−75% to −69%</td>
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<tr>
<td>Ecologic and risk area</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terai high risk (N = 4)</td>
<td>≥ 1 year</td>
<td>2006</td>
<td>864</td>
<td>11.7</td>
<td>141</td>
<td>1.9</td>
<td>−84</td>
<td>−86% to −81%</td>
</tr>
<tr>
<td>Terai moderate risk (N = 16)</td>
<td>Variable</td>
<td>2006–2009</td>
<td>348</td>
<td>1.9</td>
<td>192</td>
<td>1.1</td>
<td>−45</td>
<td>−52% to −36%</td>
</tr>
<tr>
<td>Hill moderate risk (N = 3)</td>
<td>Variable</td>
<td>2008–2009</td>
<td>28</td>
<td>2.2</td>
<td>16</td>
<td>1.3</td>
<td>−43</td>
<td>−67% to −7%</td>
</tr>
</tbody>
</table>

Japanese encephalitis expected and observed cases and incidence rates (IRs) per 100,000 person-years in Nepal.
Table 2

<table>
<thead>
<tr>
<th>Age group</th>
<th>Expected Cases</th>
<th>Observed Cases</th>
<th>Difference in IR (%)</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>All vaccinated districts (N = 23)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>19</td>
<td>2.6</td>
<td>0</td>
<td>1.2</td>
</tr>
<tr>
<td>1–4</td>
<td>167</td>
<td>5.6</td>
<td>45</td>
<td>1.5</td>
</tr>
<tr>
<td>5–14</td>
<td>513</td>
<td>7.2</td>
<td>141</td>
<td>2.0</td>
</tr>
<tr>
<td>≥ 15</td>
<td>546</td>
<td>3.5</td>
<td>154</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Vaccination target ≥ 1 years (N = 12)*

| < 1 | 12 | 2.9 | 3 | 0.7 | -75 | -95%, -27% |
| 1–4 | 137 | 8.2 | 28 | 1.7 | -80 | -80%, -70% |
| 5–14 | 407 | 10.5 | 83 | 2.1 | -80 | -84%, -75% |
| ≥ 15 | 475 | 6.1 | 93 | 1.2 | -80 | -84%, -76% |
| Total | 1,031 | 7.2 | 207 | 1.4 | -80 | -82%, -77% |

Vaccination target 1–15 years (N = 11)*

| < 1 | 7 | 2.2 | 6 | 1.9 | -14 | -69%, +87% |
| 1–4 | 30 | 2.3 | 17 | 1.3 | -43 | -67%, -9% |
| 5–14 | 105 | 3.2 | 58 | 1.8 | -45 | -58%, -29% |
| ≥ 15 | 71 | 0.9 | 61 | 0.8 | -14 | -34%, +10% |
| Total | 213 | 1.7 | 142 | 1.1 | -34 | -44%, -22% |

*N = 23; *N = 12; *N = 11

In the 12 districts that implemented immunization campaigns for the population age ≥ 1 year, the observed post-campaign JE incidence was 80% lower (95% CI = 77–82%) than the expected incidence (Table 2). Among these 12 districts, the observed incidence was 84% lower (95% CI = 81–86%) in the 4 high-risk Terai districts and 59% lower (95% CI = 48–68%) in the 8 moderate risk districts. The median difference between observed and expected incidence rates in the 12 districts was 70% lower (range = 25–100% lower). In each age group that was included in the campaigns (i.e., 1–4, 5–14, and ≥ 15 years), the observed JE incidence rate was 80% lower than the expected rate. JE incidence post-campaign was 75% lower (95% CI = 27–95%) in the < 1-year age group.

In the 11 moderate risk districts that implemented campaigns for children aged 1–15 years, the observed incidence was 34% lower (95% CI = 22–44%) than expected (Table 2). The median difference between observed and expected incidence rates in the 11 districts was 38% lower (range = 78% lower to 67% higher). In the 1–4 and 5–14 age groups, the observed JE incidence rates were 43% lower (95% CI = 9–67%) and 45% lower (95% CI = 29–58%) than expected rates, respectively. There was no significant difference between the expected and observed incidence rates in the ≥ 15- or < 1-year age groups.

Impact on AES incidence and cases. In the 23 campaign districts, the observed post-vaccination AES incidence of 7.5 per 100,000 population was 58% lower (95% CI = 56–60%) than the expected incidence of 17.9 per 100,000 (Table 3). An estimated 2,787 (95% CI = 2,690–2,883) AES cases were prevented by the vaccination campaigns. Among the 23 districts, the expected versus observed incidence showed a significant decline in 9 (39%) districts, no significant change in 10 (43%) districts, and a significant increase in 4 (17%) districts. The median difference between observed and expected incidence was 18% lower (range = 92% lower to 159% higher). Among the four districts with a significant increase in AES, three districts were adjacent districts in the central Terai, and one district was in the eastern Terai region.

As was observed with JE, the greatest impact was in the four high-risk Terai districts, where the observed AES incidence was 84% lower (95% CI = 83–85%) than expected. In the moderate risk areas, the observed post-vaccination AES incidence was 11% lower (95% CI = 6–16%) in the 16 Terai districts and 20% lower (95% CI = 6–33%) in the 3 hill districts.

DISCUSSION

Nepal’s JE immunization program from 2006 to 2009 in 23 districts had a considerable impact. Almost 900 laboratory-confirmed cases of JE were estimated to have been prevented, and post-campaign JE incidence was 72% lower than expected. In addition, because of diagnostic and logistical limitations, many JE cases are not laboratory-confirmed, and the 58% decline in clinical AES cases post-campaign suggests that the program’s impact on JE cases likely was much greater, with a total of almost 2,800 cases estimated to have been prevented in just 4 years.

The larger impact of the program in the four high-risk Terai districts was probably a result of several factors, including (1) high vaccine uptake because of sizable disease risk and increased awareness among the local population, (2) vaccination of everyone ≥ 1 year of age, and (3) availability of almost 3.5 years of post-campaign data to document impact. There are many possible reasons for the variability in the immunization program’s impact in other districts, including the lack of a significant decline in some districts. True differences may have occurred related to programmatic factors, such as coverage rates, the choice of campaign target population, or issues with vaccine handling affecting vaccine potency. However, the post-campaign observation period was also highly variable among the 23 districts, ranging from 3.5 to 40 months (median = 17.5 months). Short observation periods could have affected accurate determination of impact. In addition, in some districts, low case numbers meant there was insufficient power to detect a significant difference.

We found a significantly greater impact on JE incidence in districts that targeted vaccination to the entire population aged ≥ 1 year compared with districts that only vaccinated children aged 1–15 years. As expected, part of this difference was because of a substantial decrease in disease among adults.
aged > 15 years in the districts where they were included in the vaccination campaigns, whereas there was no significant change in JE incidence among adults in districts where they were not vaccinated. However, compared with districts that only vaccinated children, districts that included adults in the vaccination campaigns also experienced a substantially greater decline in JE incidence among children aged 1–15 years. This finding suggests that there were factors other than just the age group targeted for vaccination, such as differences in the effectiveness of campaign implementation or completeness of disease surveillance, that partially accounted for the differences in impact between these two groups of districts. For future campaigns, the decision whether to include adults should consider the number of cases and age group-specific incidence among adults.

The proportional differences between expected and observed incidence rates for JE and AES in a district were not always similar, including four districts having a significantly higher than expected post-campaign AES incidence but none having a significantly higher JE incidence. There are many etiologies of AES, including seasonal causes such as enterovirus infection or cerebral malaria, and they may influence AES patterns. Three of four districts that showed a significant increase in AES post-campaign were adjacent districts in the Terai region, suggesting that a common non-JE etiology may have been responsible for the increase. After implementation of JE immunization programs, JE cases are likely to form a smaller percentage of all AES cases. Although monitoring AES trends will generally be a good indicator of JE activity, monitoring laboratory-confirmed JE cases in the post-campaign period is also important to avoid potentially misleading information from monitoring AES trends alone.

There were several limitations with this analysis that may have resulted in an inaccurate estimate of impact. It was not possible to determine the completeness and accuracy of the routine surveillance data used or any temporal changes in reporting sensitivity. In fact, the possibility of an AES case being diagnosed with JEV infection increased during the surveillance period because of increased diagnostic testing; the percentage of AES cases with JE testing conducted increased from ≤ 70% of cases in 2004–2005 to ≥ 94% of cases in 2007–2009 (Schluter WW, unpublished data). This result could have increased the number of JE cases reported over time without a true change in disease incidence, resulting in an underestimate of the vaccine program’s impact. Other limitations included that the 6-year review period was relatively short, the accuracy of annual population estimates used for incidence calculations is unknown, there were limited post-campaign data in districts that implemented campaigns late in the period, and JE case numbers in some districts were low.

The level of JEV transmission in 2006–2009 is also unknown. Data used for the calculation of expected incidence included data from 2005, during which a large number of JE cases occurred. Immunization likely prevented human JE outbreaks in subsequent years, despite ongoing JEV transmission in the environment. A relatively consistent JEV transmission pattern is suggested by the lack of significant change in expected and observed incidence in non-target age groups (< 1 and ≥ 15 years) in districts that implemented campaigns for children 1–15 years only. A lower observed post-campaign incidence in the < 1-year age group in the districts that vaccinated all age groups ≥ 1 year may have been because of infants being protected by maternal antibody. A high number of JE cases in individuals aged ≥ 15 years before campaigns suggests that many women of child-bearing age were not immune to JE. Campaigns with high coverage likely increased immunity in women in this age group. Maternally derived JE antibody can be detected in infants for several months after birth, and therefore, a greater proportion of young infants may have been protected post-campaigns. Nonetheless, if JEV activity was higher in districts in the pre-campaign years than in post-campaign years, this analysis may overestimate the true impact of the immunization program.

Finally, the accuracy of reported campaign coverage rates could not be assessed. Although the median reported district campaign coverage rate was 94%, such coverage rates can be unreliable. A 2009 coverage survey assessed JE campaign coverage in five districts, and the median difference between survey-assessed and reported coverage was 10% lower (range = 6–26% lower) (Schluter WW, unpublished data). Lower coverage rates would have resulted in a greater percentage of the population remaining at risk and less impact on disease incidence. Other programmatic factors that could affect impact, including vaccine storage and handling at the district or local level, also could not be examined during this review.

To address some of the limitations of this analysis, it would be useful to have data from a setting in which surveillance data have been closely monitored and campaign coverage can be accurately assessed. Other Asian countries planning to implement JE immunization campaigns should ensure that they have AES and JE surveillance in place. Carefully gathered good-quality pre- and post-campaign surveillance data would be useful to refine impact estimates and provide additional information on the impact of JE immunization campaigns.

Despite the limitations, this retrospective analysis provides useful information on the considerable impact of a JE immunization program with the SA 14-14-2 JE vaccine. The findings support the belief that a substantial proportion of AES cases without laboratory confirmation is caused by JEV and that a JE immunization program will likely result in important reductions in the incidence of both laboratory-confirmed JE and clinical AES cases. In fact, overall impact on JE cases was likely about three times higher than suggested by the laboratory-confirmed cases alone. Not only are JE cases prevented, but also, the associated mortality, often as high as 20–30% of cases, and long-term disability, which may occur in 30–50% of survivors, are prevented. Immunization program managers in many Asian countries are considering introduction of JE immunization programs, and they must take into account many factors, including vaccine price, program costs, and vaccine efficacy. This information on programmatic impact will assist in the decision-making process.

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