Japanese Encephalitis: Evaluation of Vaccine Impact in Uttar Pradesh, India

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Abstract

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Japanese encephalitis (JE) virus is the leading cause of vaccine-preventable encephalitis and a significant cause of disability in Asia and the western Pacific. JE is endemic in many parts of India and the state of Uttar Pradesh (UP) contributed approximately 75% of the cases in India over the last three decades. Since 2006, UP has used the live attenuated SA-14-14-2 vaccine (CD-JEV, Chengdu Institute of Biological Products) to prevent JE. To measure the impact of vaccine introduction in UP, the number of confirmed JE cases in 1- to 15-year-old children and vaccination coverage were analyzed by year for 40 districts in UP. Vaccine-induced protection against JE seems to have come primarily from campaign coverage, with the only distinct downward trend in disease occurring in the initial 7 high-risk districts where a second high-coverage catch-up campaign targeting children aged 1- 15 years occurred 4 years after the first campaign in 2006 (p-value <0.005). There was 25% reduction in JE cases for every 10% increase in vaccine coverage in these districts. However, there was no statistically significant impact of vaccine on the number of JE cases in a combined analysis for all districts over the study time period. Limited routine immunization coverage, especially in areas where the

susceptible populations were large, was one potential reason behind inefficient vaccine impact. There is a need for catch-up campaigns in districts with poor routine immunization coverage as well as for robust routine immunization programs to sustain protection in each year’s new birth cohort.

Japanese Encephalitis: Evaluation of Vaccine Impact in Uttar Pradesh, India

Background and Significance

EPIDEMIOLOGY

Japanese encephalitis (JE) is the leading cause of vaccine preventable encephalitis and a significant cause of disability in Asia and the western Pacific. It is a zoonotic disease caused by a single-stranded positive sense RNA virus, of the family Flaviviridae (1) and vertebrate hosts such as pigs and birds play a significant role in the maintenance of JE virus in human populations (2) [Appendix 1, fig 3]. JE virus has been isolated from several species of *Culex*, *Anopheles,* and *Mansonia* mosquitoes, but *Culex tritaeniorhynchus* is the principal vector (2). JE is most common in Asian regions where rice cultivation and pig farming co-exist, as *C. tritaeniorhynchus* breeds in stagnant water (3). Humans are generally dead-end hosts as viremia in humans is rarely high enough to infect feeding mosquitoes (3).

Endemic countries encounter patterns of JE incidence that vary with climate, with peaks in late summer and autumn in temperate regions, or year-round occurrence in tropical regions and seasonal peaks during rainfalls (3). Of the five known genotypes of JE virus; Indonesia and Malaysia (I-M) are the only regions where all five genotypes can be found (4). Since genotypes 4 and 5, representing the oldest lineages, are found only in this region, JE virus is believed to have originated from the I-M region [Appendix 1, fig 2] (4).

Historically, the first case of JE was recognized in 1871 in Japan, and the JE virus (the Nakayama strain) was first isolated in the same country in 1935 (2). The geographical areas affected by JE virus have increased over the past 5 decades and JE has subsequently been reported in other eastern and southern Asian countries (3). JE spread westward into southern Pakistan for the first time in the 1990s, then into Haryana and Kerala in India respectively, and eastwards into the western Indonesian archipelago, New Guinea and northern Australia(5)

There is limited understanding in terms of how these viruses emerge and spread into new regions (5). Bird migration, global warming, changes in land usage, spread of mosquitoes by wind, and movement of infected people are thought to be some potential causes (5,6).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Within endemic countries, about 1 in 250 cases of JE infection develop clinical symptoms while the infection rates may be more clinically overt in non-Asian populations (8). With an incubation period of 5 to 15 days, most infections are either asymptomatic or mild, with nonspecific symptoms like fever, muscle aches, headache with vomiting, and gastrointestinal illness in children (7). Severe manifestations include rapid onset of high fever, headache, neck stiffness, disorientation, coma, seizures and spastic paralysis (7). Though not commonly reported in endemic areas, miscarriages can occur in women who are infected for the first time during pregnancy (7).

Acute Encephalitis Syndrome (AES) is a common manifestation of encephalitis due to JE but requires laboratory confirmation to exclude other possible causes (6). Diagnosis is most commonly made through detection of virus-specific IgM antibodies in serum or cerebrospinal fluid (CSF) (6).

IgM capture ELISA (MAC ELISA) is the most widely used diagnostic test (8). JEV-specific IgM antibodies can be detected by 4 days after the onset of symptoms in CSF and by 7 days in serum (7). There are also newer assays for early detection of JEV, such as the dipstick method and rapid IgM capture ELISA (JEVCheX, XCyton Diagnostics, Bangalore, India) (8,10). JEV-Chex has the advantage of reduced assay time and reagents for the assay are relatively more stable; however, the conventional IgM capture ELISA is still the most widely used diagnostic method (10).

MORTALITY AND MORBIDITY

The case fatality rate for symptomatic JE virus infection can be as high as 20 to 30%, while 30% to 50% of those who survive suffer significant neurological or psychiatric sequelae years later (9). Furthermore, JE is associated with immense social and financial burden in developing countries because of the neuropsychiatric sequelae, with cognitive and language impairment common among many JE survivors in developing countries (6).

An estimated 75% of JE cases occur among children less than 15 years of age in JE-endemic countries, which translates to 5.4 cases per 100,000 in this age group (11). However, there are some reports of an emerging shift to higher JE incidence in adults in countries like Japan and Korea that have controlled JE occurrence in children for decades. In areas where disease is not well controlled, the incidence remains higher in children (12).

There are no antiviral drugs for JE but supportive care can improve outcomes (10). Interventions like vector control or swine immunization may be helpful but the challenges and limitations of these strategies outweigh their benefits (9). The most effective and sustainable way to prevent JE has been human vaccination (9). A study in Thailand showed that when JE incidence was ≥3 per 100,000 population, a vaccination program at 18 months of age, with vaccines administered at the local cost of $2.16, could save $72,922 per case prevented (12). Another study from Shanghai showed that 11,946 expected cases were prevented by vaccination in a post-vaccination period between 1989-1998 where the expenditure per case prevented was 1674 yuan (US$ 265.46), with per resident expenditure to maintain the vaccination program of 200 yuan (US$ 31.71) (13). A modeling study in China predicted that the live attenuated SA 14-14-2 vaccine could prevent 427 cases and 107 deaths, resulting in saving US$ 1200 per case prevented (14).

VACCINES

The first Nakayama strain-based inactivated mouse brain-derived (IMB) JE vaccine was licensed in Japan in 1954 (15). It became the most widely used JE vaccine globally and was also included in routine immunization programs in some Asian countries (16). An overall vaccine efficacy of 91% (95% confidence interval of 70%-97%) was seen for this vaccine in China after two years of vaccination (15). However, because of concerns surrounding the temporal association of rare, but severe, neurological adverse events it is no longer in use (17).

Currently, three types of cell-derived vaccines against JE are available. These are the inactivated Vero cell-derived vaccine, the live recombinant vaccine, and live attenuated vaccines.

Immunological basis for vaccine efficacy

Protection afforded by all the vaccine types is based on stimulating the production of sufficient neutralizing antibodies. The immunological surrogate of protection is defined as seroprotection, which is a serum neutralizing antibody titre of at least 1:10, as determined in a 50% plaque reduction neutralization assay (PRNT50) (18). There is no current concern about a deficiency for cross-protection across the five genotypes (19). To date, no herd immunity has been observed with the introduction of JE vaccine (20).

Inactivated Vero cell-derived vaccine, first licensed in 1998, became the principal inactivated JE vaccine in China (17). The alum-adjuvanted vaccine based on SA14–14–2 virus strain marketed as IXIARO or JESPECT is the only vaccine used in the U.S. and other developed countries (21). Seroprotection rates as high as 99% have been observed in non-endemic settings (19). In endemic settings, seroprotection rates of 95.7% to >99% have been observed among children (22). Sustained seroprotection (90%) was noted even after 3 years in endemic settings (22) among a pediatric population. Although seroprotection can wane over time, boosters have proven to be effective to achieve sustained protective immunity (23).

Live recombinant vaccine, first licensed in Australia in 2010, is prepared by replacing premembrane (prM) and envelope (E) coding sequences of the YF live attenuated 17D vaccine virus coding sequences with analogous sequences coding the antigenic determinants from the SA 14-14-12 live attenuated JE vaccine virus (22). The vaccine has achieved seroprotection of 99.3% in children of 9-18 months old in endemic settings (30) and 95.0% in children aged 12–18 months in non-endemic settings (24). Seroprotection rates dropped from 88.5% to 68.6% after 5 years, while a single booster dose was sufficient to elicit an anamnestic response (25).

Live attenuated vaccines based on the SA 14-14-2 strain of the JE virus have been used in China since 1988 and increasingly in other Asian countries (22). A single dose of vaccine is administered at ≥8 months of age (20). Although WHO does not recommend a second dose, some countries administer a booster dose (26). Seroprotection as high as 99.3% (95% CI: 94.9–100) at 1 week–1 month (27) and 98.5% (95% CI: 90.1–99.2) at 1 year post-immunization (28) has been observed in children vaccinated at 1–15 years in settings endemic for JE. Safety studies performed in China showed a reasonable safety profile for this vaccine (29,30) and no indication of viral reversion to a neurovirulent phenotype (17). Sustained seroprotection has been observed; 98% by the end of 1 year (27) and 96% by the end of 5 years (31) after initial vaccination with a single dose in endemic settings.

CHANGES IN THE DISEASE EPIDEMIOLOGY AFTER A VACCINATION PROGRAM

JE affects all age groups, however in endemic unvaccinated areas, it is primarily a disease of childhood, as most adults in endemic areas acquire natural immunity after childhood infection (32). In areas where there are long-standing, high quality vaccination programs, JE is usually a rare disease of non-immune adults, especially the elderly (32).

RATIONALE

The actual global incidence of JE is unknown because of limitations in JE surveillance and access to adequate diagnostic facilities. An estimated 68,000 annual clinical cases of JE are reported to the World Health Organization (WHO), with approximately 13,600 to 20,400 deaths (11).

Out of 4,087 JE cases reported by 20 endemic countries to WHO in 2015, 87% of the cases were from China, India, Nepal and Vietnam (33). Furthermore, approximately 45% of these cases were from India alone (33). JE is endemic in many parts of India and spreading to newer areas where JE had never previously been reported (34). The first recorded outbreak in Uttar Pradesh (UP) was in 1978 (35) and subsequently, major epidemics have been reported from the northern and central parts of India (6).

In the past, the state of UP was found to contribute to as many as 75% of the cases in India, based on epidemiological data analyses over a period of 32 years (1978–2009) (35). The same study revealed that UP contributed a fifth of the disease burden (20.4% of cases and 18.7% of deaths) during 1978–1987, increasing to 24.3% of cases and 20.9% of deaths between 1988 and 1997, and more than half of the total cases and deaths reported between 1998 and 2009 in India (35). A major JE epidemic in Gorakhpur, UP in 2005 was associated with 6,061 cases and 1,500 deaths, reflecting 90% of all suspected JE cases and more than 89% of the deaths due to JE in India in 2005 (35). A reported 80.8%, 73.6%, 78.5% and 77.0% of all JE cases in India were from UP in 2006 and subsequent years through 2009, respectively (35). The figures were elevated because of outbreaks in Gorakhpur, UP which were associated with 2,320 cases and 528 deaths in 2006 and 3,024 cases and 645 deaths in 2007 (8).

With the ambitious plan of introducing a mass vaccination program in 104 endemic districts in 11 States in a phased manner from 2006 – 2010, India launched its first JE vaccination campaign in 2006. Based on the 2005 epidemiological data, the campaign targeted 11 of the most endemic districts in Assam, Karnataka, Uttar Pradesh and West Bengal (37). A single dose of the Chinese live attenuated SA-14-14-2 JE vaccine (Chengdu Institute of Biological Products (CDIBP), China) was administered during the campaigns to vaccinate children between 1 and 15 years of age (36). The same SA-14-14-2 JE vaccine was used for routine immunization (RI) at 9 months of age starting in 2008 while a second dose was added in 2013 under the Universal Immunization Program (UIP) (37).

Over the past 16 years, PATH, a non-governmental organization known as Programs in Appropriate Technologies and Health, has had a Japanese encephalitis vaccine project. This project has worked toward increasing the access and availability of an affordable JE vaccine to endemic countries, including India. PATH is interested in working with the WHO and other partners to measure the impact of JE vaccine on disease burden over the time period of 2006-2016 in 12 countries in the WHO South East Asia and Western Pacific Regions. As part of the overall impact assessment, India is an important country to investigate, both due to its population size as well as to the complexities that drive immunization policy and programmatic implementation. UP was chosen for this analysis because of the high burden of disease and large population size.

Primary objective

To evaluate the impact of JE vaccine upon incidence of JE among 1-15 year olds in UP, India using surveillance and immunization data that were provided to PATH by the Government of India.

Secondary objectives

There were two secondary objectives. The first was to assess and compare the mass vaccination campaign coverage with routine immunization coverage in UP over the period of 2006-2016. The second was to determine whether vaccination coverage influenced impact of vaccination on JE cases over the study time period.

METHODS

Study site

Uttar Pradesh (UP) is located in the northeast of India bordered by Nepal to the north (Fig 1, Appendix 2) (38). According to the 2011 census, UP was the most populous state in India with about 200 million population and is the fifth largest state in India with an area of 240.928 square kilometers (39,40). It has 18 administrative divisions, and 75 districts (40). The state lies in the warm temperate zone hence the summer temperatures may be as high as 43 degrees Celsius (41). A year in UP has three seasons; winter from October to February (minimum temperatures of 3–4 °C), summer from March to mid-June (temperatures up to 45 °C), and the rainy season from June to September (85% of average annual rainfall of 99cm and temperatures of 30–45 °C) (35).

The topography makes UP prone to annual flooding (35) and the five districts in Eastern UP (Gorakhpur, Kushinagar, Maharajganj, Sant Kabir Nagar and Siddarth Nagar), traversed by major rivers originating in the Nepali hills, are most prone to flooding(35). With agriculture as the main source of income (40) unorganized pig farming is a common practice in most districts in UP (35).

Surveillance and Case definitions

The JE surveillance system in India identifies patients with Acute Encephalitis Syndrome (AES) first and then confirms JEV infection through IgM ELISA testing. National guidelines for India define AES as “a person of any age, at any time of year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures). Other early clinical findings may include an increase in irritability, somnolence or abnormal behavior greater than that seen with usual febrile illness” (42). A case that meets this clinical case definition for AES is then classified as (i) laboratory-confirmed JE, (ii) a suspected case that occurs in close geographic and temporal relationship to a laboratory-confirmed case of JE, in the context of an outbreak, (iii) AES due to other agent, or (iv) AES due to an unknown agent (42). The National Vector Borne Disease Control and Prevention (NVBDCP) program defines a confirmed JE case as “a suspect case with confirmed laboratory result: detection of JE IgM in CSF or 4-fold or greater rise in paired sera (acute and convalescent) utilizing IgM/IgG ELISA, hemagglutination inhibition (HI), neutralisation test or detection of virus, antigen or genome in tissue, blood or other body fluid by immuno-chemistry, immunoflourescence or PCR” (43).

Laboratory diagnosis

Cerebrospinal fluid (CSF) and/or serum samples were tested from the AES cases for anti-JEV IgM antibodies to confirm JE using the MAC ELISA kit from the National Institute of Virology (NIV), Pune.

Data Collection

Data collection was done by PATH India from State Health Authorities as a part of the ongoing surveillance system and PATH’s technical support to the vaccination program in the state of UP.

Data Analysis

i. Determination of the impact of JE vaccination on disease over time was performed using the case report and census data from 2006-2016. Annual district-wise cumulative incidence of JE was calculated using the following formula;

JE cumulative incidence = No. of reported JE-associated AES cases in the district in year X / Population of the district under age 15 years in year X.

The annual district-wise population (denominator) was calculated based on the projected population published by the Indian government (estimated from the 2001 and 2011 census) and multiplied by the annual adjusted growth rate. An annual growth rate ranging from 1.8-3.3% across different districts was used for the period of 2006-2010. For the period of 2011 onwards, an annual growth rate ranging between 0.5-3% was used. These growth rates were estimated by the Government of India (GOI) based on the decadal growth rate from the census report of 2001 and 2011 respectively (Oral communication with PATH India) The population in the age group of 1-15 years was then calculated for each year as 33% of the annual population, based on procedures developed and employed by the Government of India (GOI)(Oral communication with PATH India).

ii. Since the vaccine was introduced in a step-wise fashion by increasing the number of districts each year starting in 2006, the first analysis was performed by creating cohorts of districts that participated in the vaccination campaign of the same year. The first cohort included 7 high risk districts which had a vaccination campaign in 2006, the second cohort included 11 additional districts which had a vaccination campaign in 2007, the third cohort included 9 additional districts with a vaccination campaign in 2008, and the fourth cohort included 7 districts with a vaccination campaign in 2009. There was one more district with a vaccination campaign in 2014 and two more with vaccination campaign in 2015; however, the follow-up data was not sufficient for the purposes of these analyses, and the last three districts were excluded from the analysis.

iii. The routine immunization (RI) data were from the State Immunization Division, Ministry of Health and Family Welfare, Government of India. The data included the number of targeted children for vaccination and the actual number vaccinated by month for each district. Vaccination coverage for each year was calculated by dividing the number of vaccinated children under 2 years by the total number of children in that age group, based on the target of immunization program. The counts were recorded on the basis of fiscal calendar which is March through April of the following year. Therefore, to account for the 3 month offset from the calendar year (25% of 12 months), the annual coverage was adjusted by subtracting 25% coverage of the given year and adding 25% coverage from the previous year.

iv. STATA/SE 14.2 was used to do the statistical analysis for vaccine impact. A multilevel mixed-effects generalized linear model (meglm) controlling for year was used to estimate the change in JE incidence as a result of vaccination. The primary outcome was the log relative risk (RR) of JE cases for each 10% increase in vaccine coverage. For this analysis, vaccination coverage was calculated as

Number of susceptible children vaccinated in year X / Total number of susceptible children in year X

The numerator was calculated by adding the number of under 2 children immunized under the RI program in a particular year to the number of immunized children <15 from the previous year and then subtracting the children who were graduating. A 2% rate based on the population pyramid of India was applied to calculate the graduating children each year who were turning 16 (44). For 2010 and 2014, the re-campaign coverage rates were higher than the RI coverage for the high risk districts, therefore the vaccination coverage rates were calculated based on the re-campaign data.

The study was declared as a non-human study by PATH's Research and Ethics Committee and therefore did not require formal review by an institutional review board.

RESULTS

Vaccination Coverage

Campaign coverage

Based on the recommendations of the Bi-Regional Consultation on JE (WHO Regional Office for South East Asia/ Regional Office for the Western Pacific) and PATH, Thailand, March-April 2005), JE vaccination was introduced in a phased-manner starting with the 7 high-risk endemic districts in 2006 in India. The live attenuated SA 14-14-2 JE vaccine was used for the vaccination campaign, which targeted children between 1-15 years old.

JE vaccination has been introduced in 39 of 75 districts in the state through 37 campaigns, the last of which occurred in 2015. The cumulative coverage for campaigns in general was high (Table 1). The exception was in 2014-15, when campaign coverage was lower and involved 1 and 2 districts respectively. The map of UP indicating the high-risk districts identified for the initial vaccination program in 2006 along with other endemic districts in which the vaccine was introduced later is presented in Figure 2, Appendix 2.

Table 1. Vaccination campaign summary in UP*

S.N.	**Year**	**No. of Districts covered**	**Target population- 1-15 years**	**Total JE vaccination campaign coverage**	**JE vaccination campaign coverage %**
1	2006	7	6,867,150	6,836,496	99.55
2	2007	11	9,220,707	9,499,157	100.00
3	2008	9	10,792,516	10,940,009	100.00
4	2009	7	8,808,547	7,837,563	88.98
5	2014	1	619,439	441,489	71.27
6	2015	2	1,409,321	571,491	40.55
Total		**37 (+2)****	**37,717,681**	**36,126,205**	83.39

*Coverage higher than 100% were rounded to 100% as per the procedure adopted by the GOI

***Two districts were covered as part of the campaign in neighboring districts.*

Routine Immunization coverage

Each initial mass campaign was followed by the integration of the vaccine into the Universal Immunization Program (UIP). The same live attenuated SA 14-14-2 JE vaccine used for the mass campaign was used for the routine immunization (RI) program. The goal was to vaccinate new birth cohorts each year who were between 9-24 months of age.

Of the 7 high-risk districts which had a vaccination campaign in 2006, one district, Siddharthnagar began the RI program vaccinating 38,708 (97%) of the children under 2 years in 2006 and 56,816 (83.39%) children in 2007. The rest of the 6 high risk districts started the routine immunization program in 2009 along with other 27 districts which had their vaccination campaigns in 2007, 2008 and 2009 as shown in table 2.

Table 2. Routine Immunization program in UP

S.N.	**Year**	**No. of Districts with campaign**	**Cumulative no. of districts with campaign**	**No. of districts with RI program**	**Average RI coverage in RI program districts (%)**
1	2006	7	7	0	0.00
2	2007	11	18	1	97.00
3	2008	9	27	1	83.39
4	2009	7	34	29	48.53
5	2014	1	35	41	40.51
6	2015	2	37	41	56.87
Total		**37 (+2)***	**39**	**41**	

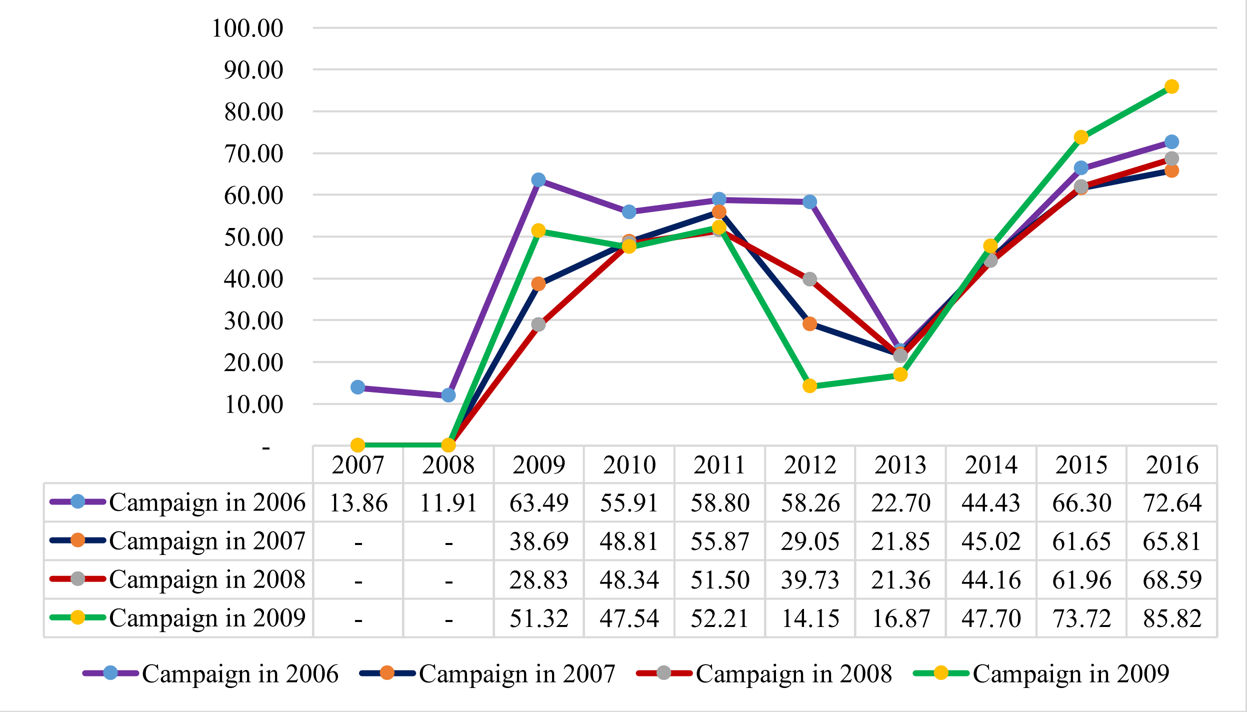
The average cumulative routine immunization coverage at the state level improved from 2.4% in 2007 to 65.2% in 2016 with a gradual improvement in immunization coverage over time as shown below in table 3 for the period between 2007 and 2016.

Table 3. Average state level Routine Immunization Coverage

Year	**#Districts**	**Mean RI coverage**	**95% C.I.**	
			Lower	**Higher**

2007	40	2.43	-2.48	7.33
2008	40	2.08	-2.13	6.30
2009	40	36.40	26.10	46.70
2010	40	41.84	32.00	51.67
2011	40	47.22	39.67	54.77
2012	40	30.80	21.87	39.72
2013	40	18.56	14.51	22.61
2014	40	40.28	33.06	47.51
2015	40	57.88	50.06	65.70
2016	40	65.20	57.41	72.99

Among the districts that introduced RI, coverage was higher in the high risk districts than in other districts from 2008-2012. Vaccine coverage fell in 2013 (Figure 2), but rose again in 2015-2016. The two cohorts that had campaigns in 2014 and 2015 were excluded from this analysis as there was not sufficient data to assess trends.



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Campaign in 2006	13.86	11.91	63.49	55.91	58.80	58.26	22.70	44.43	66.30	72.64
Campaign in 2007	-	-	38.69	48.81	55.87	29.05	21.85	45.02	61.65	65.81
Campaign in 2008	-	-	28.83	48.34	51.50	39.73	21.36	44.16	61.96	68.59
Campaign in 2009	-	-	51.32	47.54	52.21	14.15	16.87	47.70	73.72	85.82

Fig. 2 Average RI coverage in % by campaign cohorts

The vaccination coverage in the 7 high risk-districts dropped from 98.6% in 2006 when the vaccination campaigns were initiated to as low as 0.68% in 2009 when vaccine coverage was calculated as described above. The catch-up campaign in 2010 increased the coverage to 84.3% as shown below in Fig 3.

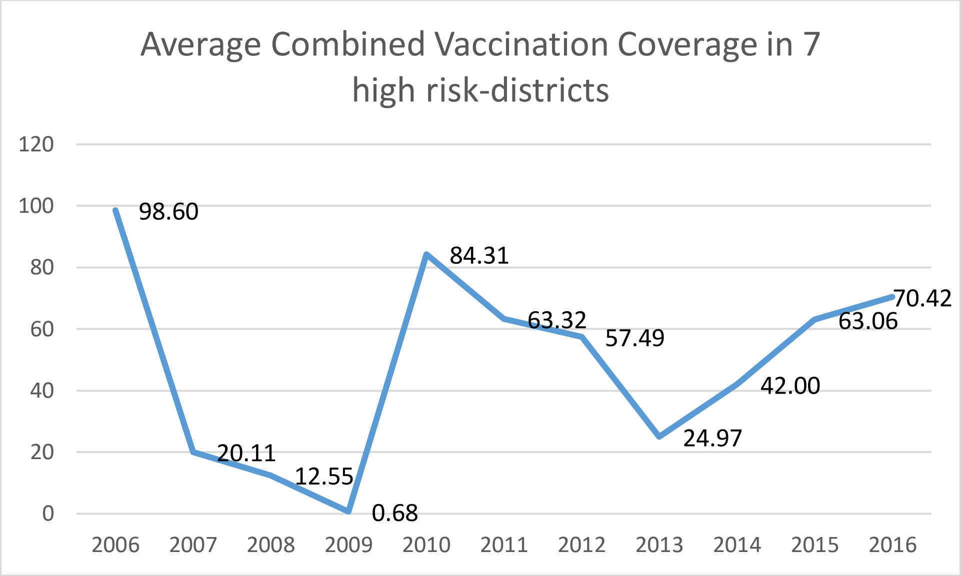


Fig 3. Combined vaccination coverage from campaign and RI program in the 7 high-risk districts

Second dose of JE vaccine

For the 39 districts which introduced RI, a two-dose vaccination policy was introduced into the program in 2013. It appears that the second dose coverage was slightly higher in 2013 and 2014 but lower than the first dose in the following years (Figure 4).

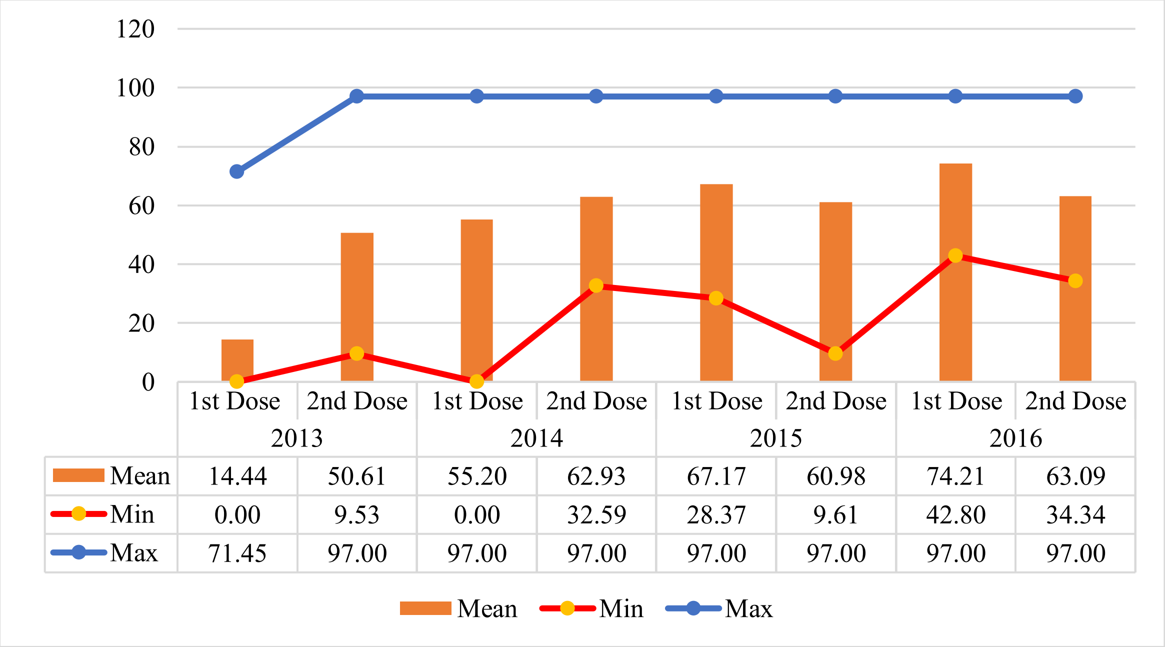


Fig 4. RI first and second dose coverage after the second dose policy introduction

Analysis by campaign year

Over the 10-year time period between 2006 to 2016 the incidence rate of JE in the age group of 1-15 years rose from 118 per 10 million population in 2006 to about 400 per million in 2009 per 10 million and decreased to 100 per 10 million in 2016 in the 7 high risk districts (Figure 4). These districts had their first vaccination campaign in 2006 and a second campaign in 2010. The first vaccination campaign in 2006 covered 6,867,150 children between 1-15 years old, translating into a coverage of 98.72% and the 2010 re-campaign vaccinated 6,724,732 children of the same age group with a coverage of 98.81%. This would have amounted to a first dose for the 4 birth cohorts born between 2006 and 2014 and a second dose for those previously immunized in 2006 excepting children who were older than 15 years by 2010. In an analysis combining all districts, there was Further **statistical analysis** revealed that though there was no evidence of vaccine effect for all districts in a combined analysis (p=0.7) there was a statistically significant reduction in JE cases

($p<0.005$) in the initial 7 high-risk districts. The number of JE cases declined 25% for every 10% increase in vaccine coverage.

A comparative analysis of districts grouped into cohorts based on the vaccination campaign year is presented below (Fig 4) and in Table 1, Appendix 3. Although the trend is inconsistent, the disease incidence seems to have the steepest drop in 2010 for the first 7 districts that initially introduced vaccination in a mass campaign in 2006. In contrast, the cohorts that introduced vaccination with single campaigns in 2007 and 2008 demonstrated an upward trend in disease incidence in 2010. The cohort of districts that introduced JE vaccine by campaign in 2009 demonstrated a relatively flat trend in disease incidence through 2012, after which incidence increased.

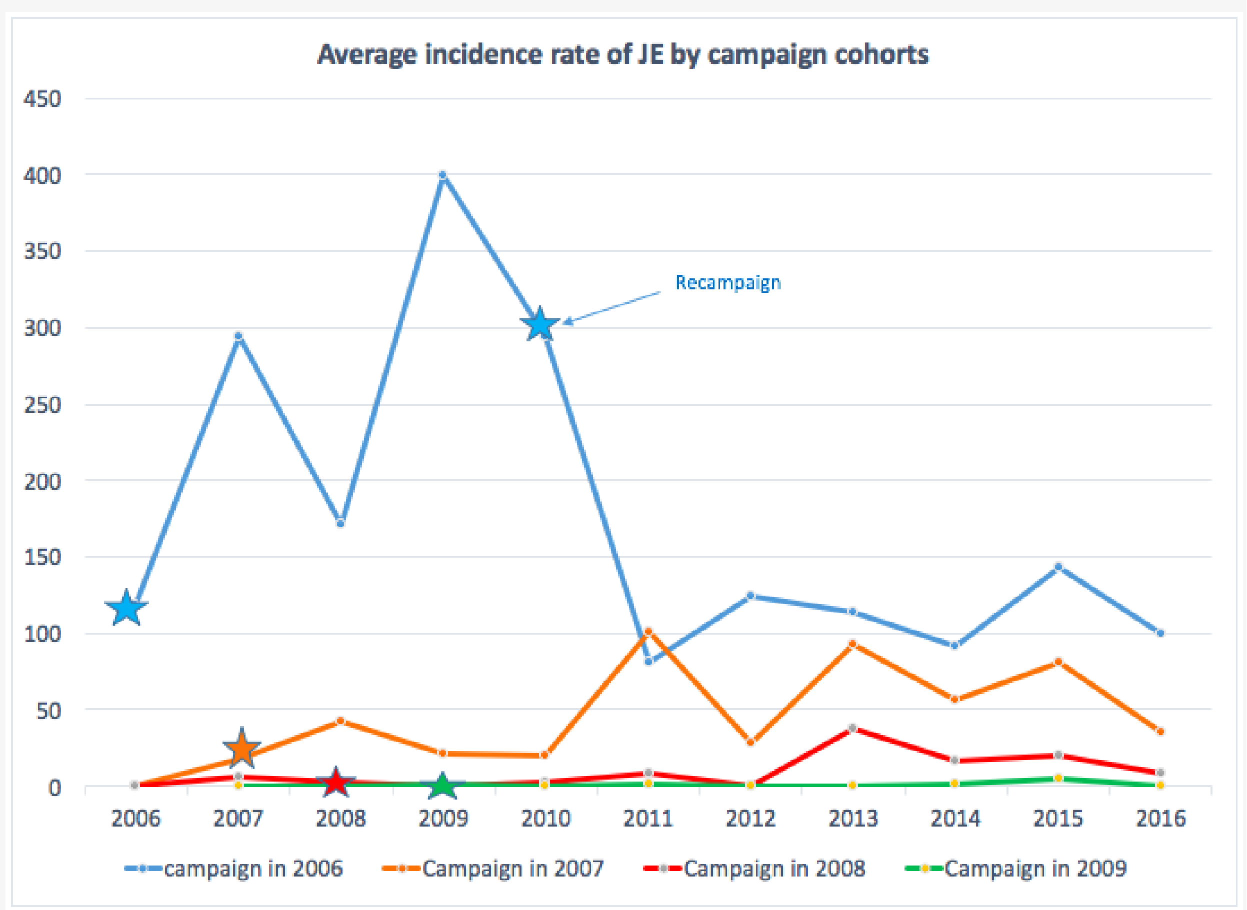


Fig. 4 Average incidence rate of JE for campaign cohorts per 10^6 children between 1-15 year old

* Star represents the vaccination campaign year

DISCUSSION

Vaccine-induced protection against JE seems to have come primarily from campaign coverage, with the only distinct downward trend in disease occurring in the initial high-risk districts where a second high-coverage catch-up campaign targeting children aged 1- 15 years occurred 4 years after the first campaign in 2006. Districts that were added later had smaller disease burden at the beginning and with single campaigns the disease rates did not drop dramatically.

The JE vaccination campaigns covered 39 of 75 districts in the state of UP. The vaccination coverage during campaigns was consistently high during the first five years after campaigns were introduced, including the second campaign for the first cohort of high-risk districts in 2010. The vaccine was introduced in 41 districts under the RI program and the coverage was poor in general. Only the high-risk districts were able to maintain an average coverage of more than 50% until 2012.

The failure of the vaccination program to significantly reduce risk of JE may be due to the limited RI coverage. Poor RI coverage in a country which has one of the largest birth cohorts in the world with 27 million new births each year (45) means that each year the state was getting a large new cohort of unimmunized children who were exposed to JE virus resulting in many new cases. This may partly explain the high JE incidence rate over the years, despite high coverage in periodic mass vaccination campaigns in the early years.

The RI coverage was lowest in 2013. Interestingly, that was the year that the two-dose vaccine policy was introduced in an attempt to increase the overall poor coverage with the first dose given in RI. By administering a second dose, the goal was to immunize children who missed the first dose. Therefore, one possible explanation behind the low vaccine coverage in 2013 could be the two-dose JE vaccine strategy that was introduced under the UIP, with the first dose (JE) to be given between 9 and 12 months along with measles-containing vaccine and second dose during 16-24 months along with DPT/OPV booster and second dose of MCV (46). According to personal communication with PATH India staff who supported the program, there was confusion among the healthcare providers following the two-dose policy introduction in the state. Both health care providers and parents were not confident that vaccinating their children with multiple vaccines at once was safe, despite the fact that co-administration of JE vaccine with other vaccines had demonstrated an acceptable safety profile (47). The same reason may have occurred during the 2014 and 2015 though we cannot fully know the degree to which the policy change could have affected the campaign coverage.

Apart from the confusion associated with this change in vaccination policy, there were some logistical challenges in the early years of vaccine introduction. According to unpublished reports by PATH (2008 and 2009), the initial RI program depended on the buffer stock of vaccine used after the vaccination campaign. Health care providers completely ceased routine immunization when they ran out of vaccine stock. Additionally, issues like lack of clarity of guidelines for introduction of JE vaccine in RI, lack of clarity of roles and responsibilities of UIP and VBDC divisions, communication gap and weak coordination between the districts and the States, along with issues with delayed JE Vaccine supply were barriers to the RI program in the first few years.

However, on a positive side, the average RI coverage at the state level seems to have improved in recent years. This might explain why the coverage for the second dose of vaccine in our study seems to be higher than what has been reported by other studies in the past (48).

The incidence of JE over the 10-year period seems to have fluctuated with no predictable trend. This is common for a mosquito-borne disease like JE. However, the increasing trend in JE, especially in the cohort living in the high-risk district seems to have followed a downward trend after 2010 after a second catch-up campaign. The importance of vaccination campaigns and catch-up campaigns to compensate for low RI coverage has been demonstrated in other countries. A study done in Ecuador found that campaigns increased the routine immunization coverage of children under 5 years from 43% to 64% (49).

In Nepal, a country physically adjacent to UP, which uses the same vaccine and strategy of vaccine introduction as in UP, the vaccine impact was most pronounced in the high-risk districts (50). The authors concluded that this could have been due to high vaccine uptake because of sizable disease risk and increased awareness among the local population, and vaccination of the susceptible population ≥1 year of age through the primary mass campaign (50). Since the high risk districts in UP had significantly higher disease incidence as compared to other districts, with several outbreaks in the past, the attribution of the disease risk and vaccine uptake might be true in this study as well. The same factor might have driven relatively more routine coverage as compared to other districts.

Mass vaccination campaigns offer the opportunity for clear communication between service providers and caregivers during door-to-door visits. The face-to-face interaction focused on a single health issue could motivate caretakers to accept vaccination of their children, whereas this might not be possible during routine programs. In fact, monitoring and evaluation reports by PATH have remarked on a hesitancy of caretakers or health care providers to vaccinate children with multiple vaccines on the same day, even though recommendations indicate that JE vaccine should be given with other childhood vaccines under the UIP (47).

A few years ago, researchers noted that although JE was regarded as a deadly disease, it was not considered a major health problem by community and health care providers in Kushinagar, UP because other diseases were more common (47). This belief may explain why community members and health care workers do not feel the need to take the JE vaccine seriously during the RI program.

Since a qualitative study by other researchers in UP had shown that there is no social or cultural resistance against JE vaccination (51) there is an opportunity to improve routine immunization coverage in new birth cohorts. Re-campaigns in districts with poor RI coverage could be the starting point followed by universal coverage of all susceptible children through a strong RI program could help reduce the incidence of JE. In the absence of sufficient reasons behind low RI coverage, an in-depth study of the issues behind the poor vaccine uptake in the RI program seems important especially because UP accounts for 75% of the JE cases in the country for the last three decades between 1978–2009 with multiple outbreaks and thousands of deaths (35).

A limitation that cannot be ignored in the comparative analysis includes the variation in the post campaign observation period across district cohorts which ranged from 4 years to 10 years. This is why the last two cohorts were excluded from the comparative analysis.

Since UP has the poorest average coverage of childhood vaccination in India (45), the pre-existing public health system might have also influenced the poor RI coverage in UP. In the past, polio campaigns demonstrated that in geographical regions burdened by the most challenging social and health systems, it is important to strengthen health systems and address social challenges apart from, and in addition to, focusing on the vaccination campaign (52). Since people are still ignorant about the causes and routes of transmission of disease (51) it also highlights the fact that apart from vaccination, improvement in vector control, sanitation and hygiene are also important (48). Furthermore, malnutrition is a major problem in India, especially in children, meaning that even vaccinated children may be at increased risk of poor immune response to vaccination secondary to malnutrition (53).

Finally, another reason behind the JE disease rate not decreasing could be attributed to the improvement in the surveillance system over time. According to PATH, there were 15 sentinel sites in UP in 2010, which increased to 23 in 2017 through joint efforts of the government of India and US CDC. Improved reporting may have captured a greater proportion of the true number of cases in later years.

In the absence of testing anti-JEV IgM positive cases for anti-dengue (DENV) IgM antibodies, it is possible that cases of JE-associated AES could have been overestimated. On the other hand, the data we used includes only reported cases, so unreported cases and/or cases that did not result in AES might have been missed. On the other hand, testing for possible causes of AES including scrub typhus, herpes, dengue and bacterial meningitides to rule out non-JE associated AES cases seems important (54,55).

There might also have been inaccuracies associated with the annual population estimates used as the denominator for JE incidence rate calculations. However, while this may have impacted the precision of the estimates, because we used the same method of estimation across all years, any error would have affected calculations equally for each time period, making it still possible to observe trends.

The sample type used to confirm JE infection was not consistent across the districts and over time; CSF was used in some and serum in others. Furthermore, the sensitivity and specificity of the NIV kit used in UP has been found to have variable values with CSF and serum (sensitivity of 75% in CSF, and 71% in serum and a specificity of 96% in CSF and 77% in serum) (56). However, the study period is so long that the misclassification due to average sensitivity and specificity of JE diagnosis is probably consistent over the years.

Importance of the findings as they relate to PH

The data came from an established large-scale population-based surveillance system covering different geographical locations where the surveillance data have been closely monitored and improved since the introduction of vaccination. This enhances confidence in our findings. To our knowledge, this study is the first to evaluate the population-level impact of JE vaccination over more than a decade**.** Despite several limitations, we believe that the decade-long period of time for assessment has helped to shed light on the disease trends over time - reflecting the need for catch-up campaigns in districts with poor RI coverage as well as the need for robust RI programs to sustain protection in the new birth cohorts each year. Only then can the potential impact of vaccination be maximized in the state.

CONCLUSION AND RECOMMENDATIONS

Vaccine-induced protection against JE seems to have come primarily from campaign coverage, with the only distinct downward trend in disease occurring in the initial 7 high-risk districts where a second high-coverage catch-up campaign targeting children aged 1- 15 years occurred 4 years after the first campaign in 2006 (p-value <0.005). Limited routine immunization coverage, especially in areas where the susceptible populations were large, was one potential reason behind the apparent lack of statistically significant impact of vaccine on the number of JE cases in most of the districts over the study time period

Furthermore, multiple vaccination campaigns of this type are considerably inefficient compared to initial campaigns and subsequent establishment of high coverage RI. Sustaining high levels of immunity among each year’s new birth cohort will require routine immunization in addition to vaccination campaign. Building on the disease monitoring system, ensuring vaccine availability at the primary health care centers and districts and developing mechanisms to sustainably reach the majority of the target population is of primary importance for the success of a routine immunization program against JE. There might be other underlying factors associated with the limited RI coverage which were beyond the scope of this study. Exploration of those factors seems crucial to strengthen the ongoing vaccination program in UP.

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APPENDICES

APPENDIX 1

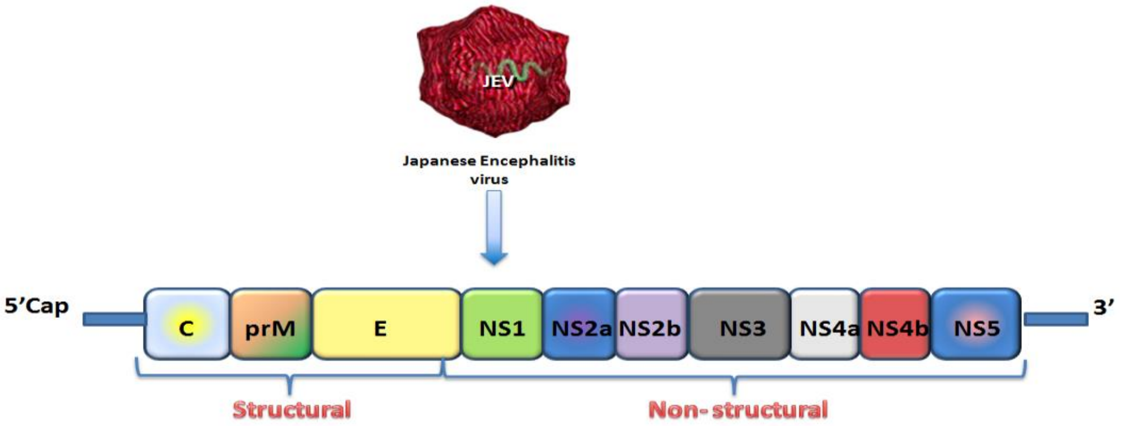
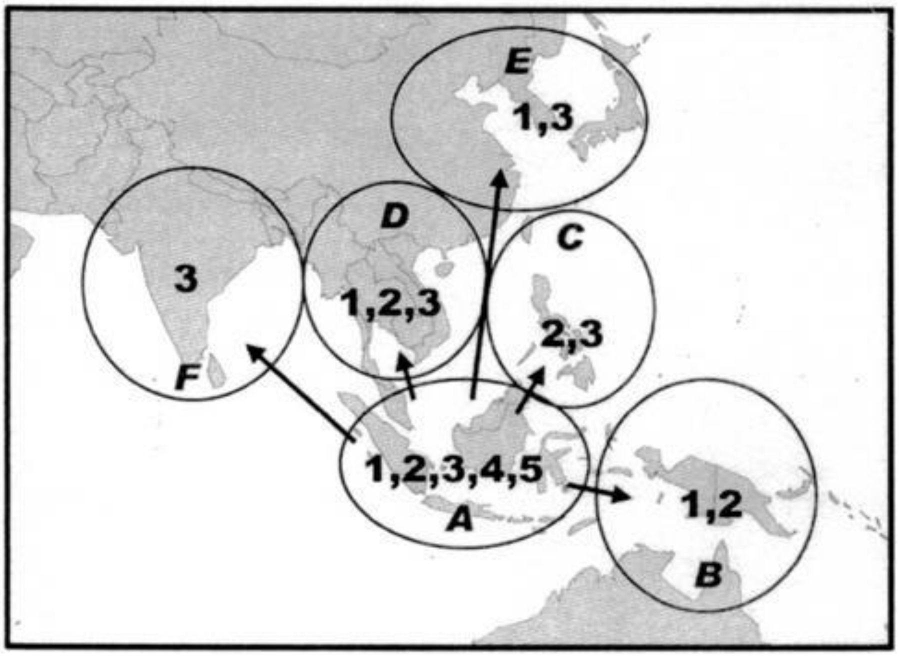


Fig 1: Japanese Encephalitis Virus genome (3)



Abbreviations: A - Indonesia (excluding New Guinea) and Malaysia; B - Australia and New Guinea; C - Taiwan and the Philippines; D - Thailand, Cambodia, and Vietnam; E - Japan, Korea, and China; F - India, Sri Lanka, and Nepal. Region A contains all the genotypes including genotypes 4 and 5, whereas other regions contain more recent genotypes.

Fig 2. Distribution of Genotypes of JE virus (4)

Appendix 2

Fig 1. UP in the map of India (43)

MAP OF AFFECTED DISTRICTS

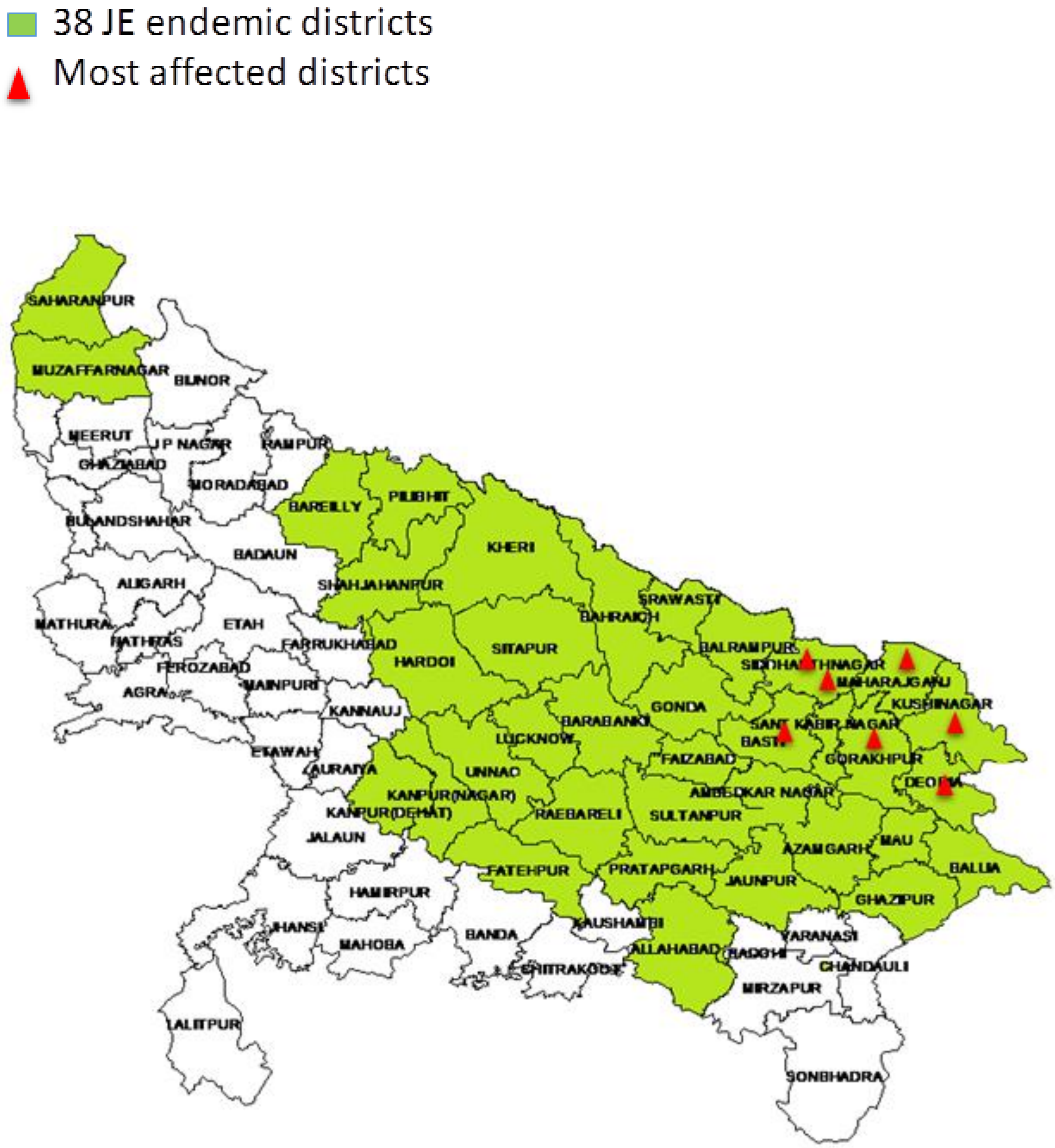


Fig. 2 Map of JE affected districts (PATH India)

Appendix 3

Table 1. Incidence rate per 10 million children in the children1 to 15 year by campaign year

Year	Campaign in 2006	Campaign in 2007	Campaign in 2008	Campaign in 2009
2006	118	0	0	0
2007	293	18	5	0
2008	171	42	3	0
2009	399	20		1
2010	293	20	2	0
2011	80	101	8	1
2012	124	27	0	0
2013	113	92	37	0
2014	91	56	16	1
2015	142	81	20	4
2016	99	35	9	0